# The art of balance

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*DOI:*
10.33612/diss.101445743

# THE ART OF BALANCE

## ACUTE CHANGES IN BODY COMPOSITION DURING CRITICAL ILLNESS

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Publication of this thesis was financially supported by the University Medical Centre Groningen, the University of Groningen, and the Graduate School GUIDE of the University of Groningen.

Cover design and lay out by Ellen Beck
Printed by Ipskamp Printing
ISBN 978-94-034-2054-7 (printed version)
ISBN 978-94-034-2055-4 (digital version)

rijksuniversiteit
groningen

# The art of balance

Acute changes in body composition during critical illness

**Proefschrift**

Ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het college voor promoties

De openbare verdediging zal plaatsvinden op

woensdag 27 november 2019 om 16:15 uur

door

**Lara Hessels**

Geboren op 9 augustus 1991
te Zwolle

**Promotores**
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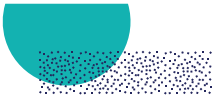



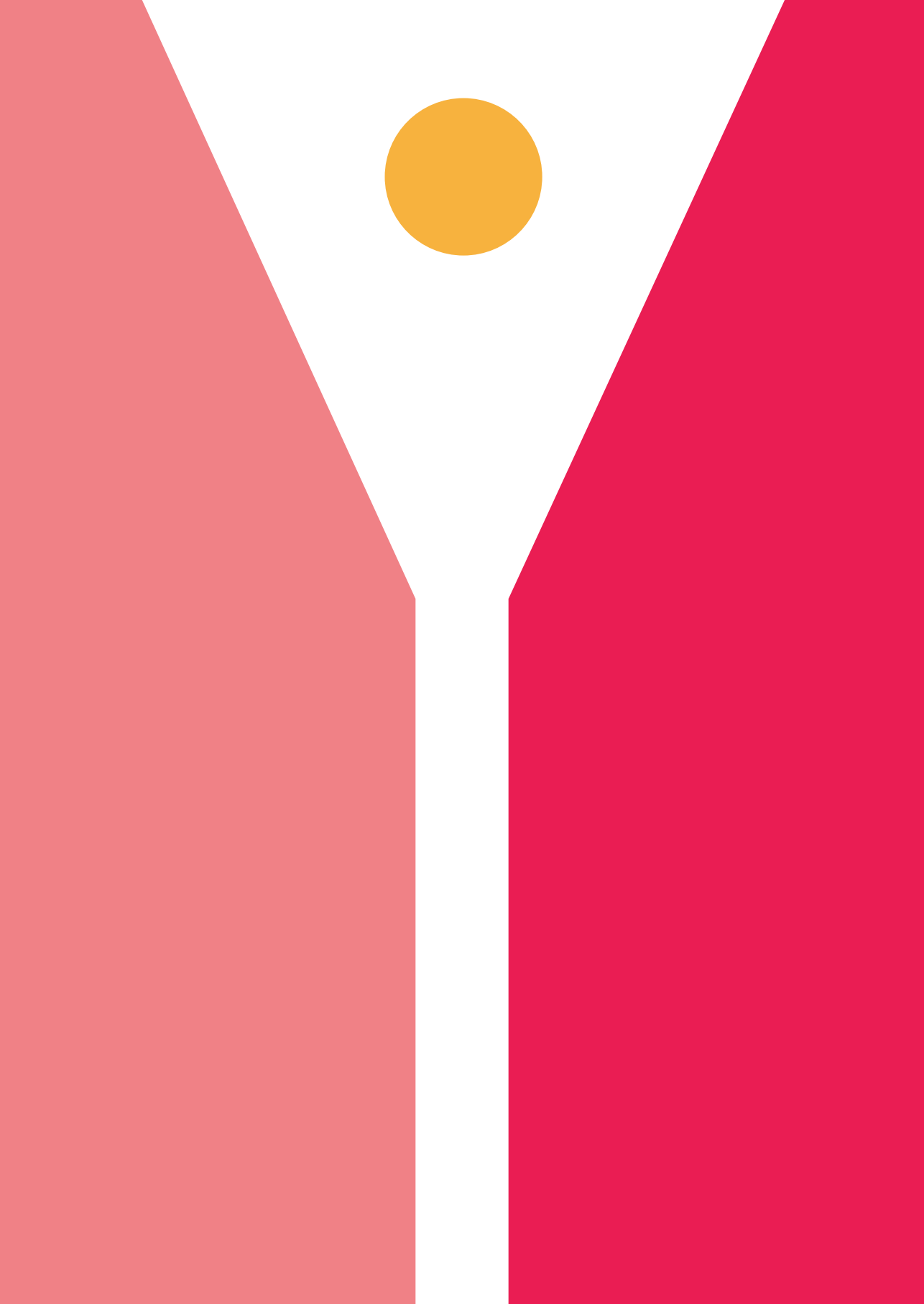

# CHAPTER 1

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## GENERAL INTRODUCTION

*"La fixité du milieu intérieur est la condition de la vie libre et indépendante"*

- Claude Bernard

Challenges are all around us in everyday living and stress helps us to cope with changes in our surroundings, as well as with internal stressors. The response to stress is an elaborate mechanism that has evolved over millions of years and exists in all animals. Although it is an important and basal mechanism, it is not yet fully understood. Throughout history, many scientists have tried to get a better understanding of the concept and mechanisms of stress.

In the 19th century, Claude Bernard introduced the concept of a milieu intérieur (a stable internal environment) where animal cells are kept constant through bodily compensatory mechanisms [1]. He stated that the constancy of the intracellular environment was an essential condition for life and should be restored rapidly to survive serious derangements. This concept evolved further by the work of Walter Bradford Cannon who named it homeostasis. Illness would occur when homeostatic systems failed to keep physiology within normal values [2].

David Cuthbertson observed loss of lean body mass in patients after trauma. These patients had a higher urinary excretion of intracellular components, such as nitrogen, potassium and creatinine [3]. Cuthbertson hypothesized that trauma patients used the protein derived from their lean body mass as an energy source. He later described the metabolic response to severe stress as three phases, i.e., the ebb phase, the initial flow phase and the late flow phase. The ebb (shock) phase starts with a decrease in metabolic activity, increases in blood glucose and sodium retention. The flow (post-shock) phase starts after 3 to 10 days when an increased catabolic state leads to a negative nitrogen balance, proteolysis and decrease in fat stores. The excretion of intracellular components is markedly increased during this phase. When patients start to improve, the flow phase ends and the catabolic state is reverted to an anabolic state [4]. Later, other scientists have defined these three phases differently, but they can all be summarized as an acute phase, an established phase and a recovery phase with the goal to restore homeostasis [5].

## HUMAN BODY COMPOSITION

Homeostasis is maintained by keeping a relatively constant volume and composition of body fluids. Two compartments can be distinguished to where the key electrolytes are distributed: the extracellular volume (ECV) and the intracellular volume (ICV). The ECV can be further divided into the interstitial compartment and the plasma volume. The ECV covers around 43% of the body fluids, whilst the ICV makes up around 57% of the total body fluid [6].

The percentage total body fluid or total body water (TBW) varies per person [6-8]. In an average man, the TBW is about 60 percent of his body weight. Skeletal muscle mass accounts for a large part of TBW and makes up 40 to 50% of TBW. The percentage of TBW depends on age, gender and degree of obesity [6]. Total body water normally decreases with age, mainly because of an increase in fat percentage and a decrease in skeletal muscle mass. As women usually have a greater fat percentage as well, their TBW is lower and is around 50 percent of their total body weight. Babies on the contrary have a higher TBW, which is around 70 percent of their body weight [9,10](Figure 1).

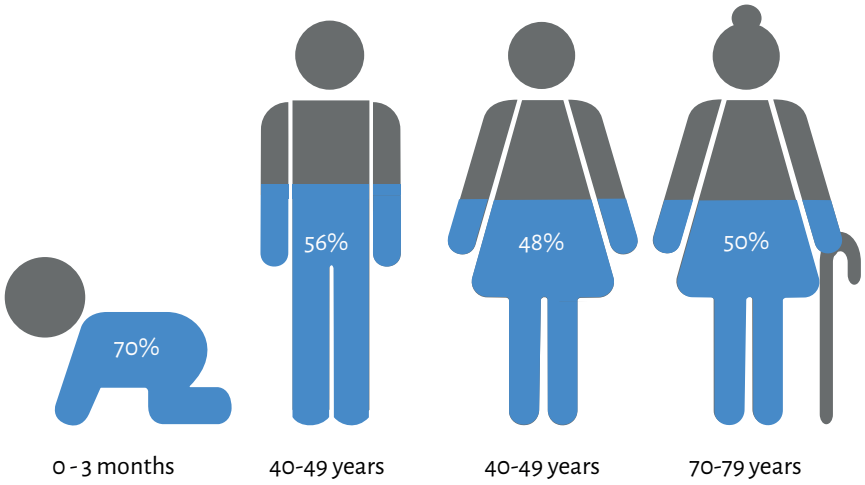


**Figure 1. Age and sex and total body water.**
Total body water is depicted in blue and in percentages. All values are depicted for Caucasian subjects [7,9,10]. Infants have a considerable higher TBW percentage. Men also have a higher TBW percentage compared to women, mainly because they have more muscle mass and less body fat. As a person gets older, the TBW decreases.

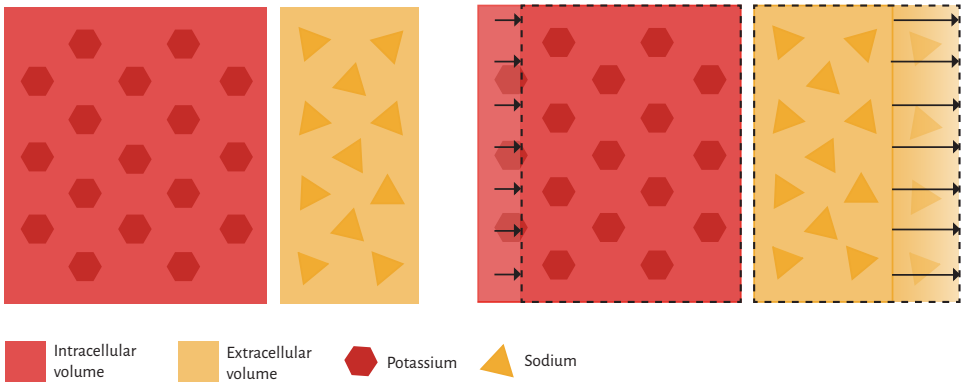


**Figure 2. Fluid compartments and electrolyte distribution.**
In red the ICV is depicted, with its major cation potassium. In yellow the ECV (including plasma and interstitium) is depicted, with its major cation sodium. Water, potassium and sodium can be exchanged between the ICV and ECV. The left image depicts the normal distribution of water, potassium and sodium among the compartments. In an average man, the ECV is around 43% of the TBW and the ICV is around 57% of the TBW. The ICV is mainly skeletal muscle mass. The right image depicts the loss of muscle mass as it occurs in critically ill patients. As skeletal muscle mass makes up 75% of all cells, this leads to a reduction of the ICV. At the same time, the ECV increases, due to sodium and fluid retention. Adapted from Guyton, et al. [11].

The ECV and ICV are separated by cellular membranes and have a different composition of electrolytes. The major cation of the ECV is sodium. Almost 98% of total body sodium resides in this compartment. Potassium is the major cation of the ICV and mirrors sodium with around 95% of total body potassium located in the ICV (Figure 2). Both are the principal determinant of the osmolality in their respective compartment and both are related to the volume of water in their compartment.

## CHANGES IN HUMAN BODY COMPOSITION

As Cuthbertson already observed, the stress response accompanying critical illness leads to loss of lean body mass, especially of skeletal muscle mass [12]. Lean body mass can be defined as the fat free mass of the body. Critically ill patients can lose more than 10% of lean body mass in the first week of intensive care unit (ICU) admission. ICU survivors consequently often experience significant skeletal muscle weakness, which can persist for more than 5 years [13]. It is therefore not surprising that muscle wasting in critically ill patients is associated with increased morbidity and mortality [13,14].

Muscle mass is maintained by a balance between protein synthesis and breakdown. Wasting or catabolism occurs when there is a net loss of protein, as occurs in times of stress such as critical illness, under the influence of stress hormones and inflammatory mediators. Immobility and systemic inflammation lead to a decreased protein synthesis [13]. In critically ill patients the severity of injury, increase of pro-inflammatory cytokines, oxidative stress and exogenous glucocorticoids all contribute to muscle wasting [15].

The increase in protein turnover during critical illness is coupled to an increase in gluconeogenesis and loss of nitrogen. Nitrogen balances are therefore often used as a reflection of protein balance [16]. However nitrogen balances also have shortcomings and will generally result in an overly positive balance, which leads to an underestimation of protein requirements [17].

Catabolism, and thus changes in the body composition, could possibly also be assessed by another technique. Muscle wasting leads to a decrease in body cell mass (BCM). BCM is the totality of all cells in the body and the metabolic active compartment of lean body mass [18]. BCM is larger in males compared to females, again because males usually have a larger skeletal muscle mass. BCM is proportional to total body potassium. Therefore, the golden standard to measure BCM is the measurement of total body potassium (TBK) with 40K scintigraphy [18,19].

## POTASSIUM

The ease of measurement of the extracellular sodium concentration, is the exact opposite of that of intracellular potassium [20]. Although, TBK can be assessed by 40K scintigraphy [18], it is a cumbersome method that is not very suitable for bedside measurements. TBK and thus BCM is known to decline during muscle wasting. However, one can argue that in order to detect or quantify a decrease in BCM, which in critically ill patients will often be due to catabolism, only measuring the change in BCM and thus the change in TBK is sufficient. A method to identify such changes is to perform balance studies. Balances are defined as the difference between the total output and the total intake. A negative balance indicates a loss. Net potassium loss under a constant serum concentration can only originate from the ICV [21]. In various patients groups experiencing loss of BCM, such as surgical, burn and pediatric patients, negative potassium balances have been observed [22-26]. Balance studies could therefore be a feasible approach to determine changes in TBK and thus BCM [20].

## SODIUM

The most notable and rapid change during the catabolic state that accompanies acute critical illness is an increase of the ECV because of sodium and fluid retention [6, 27]. During treatment in the ICU, patients receive large amounts of sodium-based fluids as part of their resuscitation therapy to minimalize vascular leakage. This can lead to sodium accumulation and iatrogenic hypernatremia. Hypernatremia may result in increased morbidity and mortality and this complication of the intravenous therapy is thus not without risks. Moreover, the generally accepted model on sodium homeostasis, which states that sodium is distributed among only two compartments (i.e., the ECV and the ICV) has been challenged. Recent studies have suggested that sodium can also accumulate without weight gain or hypernatremia in a sub-compartment of the extracellular compartment [28]. Whether this also occurs in critically ill patients and if this sub-compartment is altered by critical illness has not yet been studied.

## CREATININE

Creatinine is the stable end product of creatine, which is predominantly present in muscle where it is converted to creatinine in a steady rate. After creatinine is released into the circulation, it is almost completely excreted in the urine [29]. In steady state conditions, urinary creatinine excretion will therefore be equal to creatinine production, irrespective of circulating creatinine. Twenty-four hour urinary creatinine excretion is almost perfectly correlated with lean body mass, as assessed by $^{40}K$ studies [30].

In stable outpatients, measurement of creatinine excretion in 24-hour urine collections is a widely accepted method for muscle mass estimation and creatinine clearance [24, 31-33]. Although it has not been well studied in critically ill patients, a decrease in creatinine excretion has been observed in ICU patients after seven and fourteen days of ICU stay [34], which may be a reflection of the muscle loss these patients experience. In other patient groups, such as chronic kidney disease patients, it has been proposed that UCE might be a suitable marker to quantify the decline in muscle mass [32].

## OUTLINE OF THESIS

This thesis focuses on acute changes in the composition of the fluid and electrolyte compartments in critically ill patients and aims to get a better understanding of the biochemical derangements in critically ill patients during these changes.

Potassium homeostasis is often disturbed during critical illness and such disturbances can induce severe complications such as cardiac arrhythmias and death [35].
After the observation of a potential beneficial effect of tight glucose control [36], our ICU introduced a nurse-centered, computerized decision support glucose regulation protocol (GRIP, glucose regulation in intensive care patients) in 2004 [37, 38]. As potassium regulation has many similarities with glucose control, a potassium regulation algorithm was integrated within GRIP (GRIP-II, glucose and potassium regulation in intensive care patients) [39].
In **Chapter 2**, we evaluated the relation between serum potassium, potassium variability and in hospital mortality during ICU admission as well as the effect of computer-driven potassium regulation.

As previously stated, potassium derangements can induce cardiac arrhythmias [35]. However, it is unknown if subtle changes within the normal range can also affect the incidence of atrial fibrillation. The GRIP-COMPASS trial compared the incidence of atrial fibrillation between two serum potassium targets that were both within the normal range in cardiac surgery patients. The results of this prospective study are described in **Chapter 3**.

After we discovered consistent negative potassium balances in GRIP-COMPASS patients which we did not fully understand, we further explored this in **Chapter 4**. In this chapter, we closely examined the fluid, sodium and potassium balances in cardiothoracic ICU patients. It is known that the initial days of ICU admission are accompanied by sodium and water retention and thus an expansion of the ECV [40]. However, the potassium balance and thus the change in the ICV of critically ill patients has not yet been studied.

The stability of the ICV is likely to be important for all organs of the body and the ability to maintain or regain stability of the ICV probably also influences the viability of an organ after transplantation. In **Chapter 5** we evaluated potassium and sodium shifts during reperfusion of transplanted livers in both ex vivo and in vivo models and its relation with the viability of the liver graft.

Cachexia as a comorbidity is not only seen in critical illness. Heart failure patients constitute only one of the many patient groups that also suffer from this comorbidity. Survival of heart failure patients has greatly improved after the addition of potassium-sparing agents, such as

ACE inhibitors and spironolactone, to conventional treatment [41,42]. In **Chapter 6**, we postulate that the beneficial effects of these agents partly result from preserved total body potassium with consequent muscle mass preservation.

Critical patients are at risk of developing both hyponatremia and hypernatremia. Both can be caused by factors associated with critical illness, such as reduced urinary concentrating ability, increased insensible losses and increased activity of antidiuretic hormone. However, iatrogenic causes such as fluid administration and drugs are also associated with the development of sodium derangements. Both hyponatremia and hypernatremia are associated with a higher morbidity and mortality in critically ill patients. In **Chapter 7** we analysed long-term changes in the incidences of sodium derangements and their association with therapy shifts over the course of twenty years.

Conventionally, sodium homeostasis is explained by a two-compartment model with intracellular and extracellular compartments where ions are completely dissolved, i.e., osmotically active. Recently, a sub-compartment of the extracellular compartment has been proposed [28] over which sodium is stored nonosmotically active without causing a volume expansion of the extracellular compartment. As critically ill patients receive large amounts of sodium-based fluid, we studied in **Chapter 8** whether sodium is stored in such a compartment in critically ill patients.

Muscle mass plays an important role in the ability of critically ill patients to overcome their disease. A low muscle mass is associated with morbidity and mortality in critically ill patients [13,43]. However, muscle mass is difficult to quantify in ICU patients. In **Chapter 9** we investigated the relation between baseline urinary creatinine excretion, as marker of muscle mass, with short- and long term outcome in ICU patients.

Although a decrease in UCE has been observed in ICU patients after prolonged ICU admission [34], the time course of UCE has not been described in detail in this patient group. Muscle wasting may be expected to lead to decreases in serum creatinine as well. Therefore, eGFR and creatinine clearance equations that use serum creatinine as input variable may become unreliable during ICU admission. In **Chapter 10** we described the time course of urinary creatinine excretion, measured creatinine clearance and estimated glomerular filtration rate over the course of 30 days of ICU admission.

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# CHAPTER 2

## THE RELATIONSHIP BETWEEN SERUM POTASSIUM, POTASSIUM VARIABILITY AND IN-HOSPITAL MORTALITY IN CRITICALLY ILL PATIENTS AND A BEFORE-AFTER ANALYSIS ON THE IMPACT OF COMPUTER-ASSISTED POTASSIUM CONTROL

**Critical Care 2015;19:4.**

Lara Hessels, Miriam Hoekstra, Lisa J. Mijzen, Matthijs Vogelzang, Willem Dieperink, Annemieke Oude Lansink, Maarten W. Nijsten

# ABSTRACT

## INTRODUCTION

The relation between potassium regulation and outcome is not known. Our first aim was to determine the relationship between potassium levels and variability in (ICU) stay and outcome. The second aim was to evaluate the impact of a computer-assisted potassium regulation protocol.

## METHODS

We performed a retrospective before-after study including all patients >15 years of age admitted for more than 24 hours to the ICU of our university teaching hospital between 2002 and 2011. Potassium control was fully integrated with computerized glucose control (glucose and potassium regulation program for intensive care patients (GRIP-II)). The potassium metrics that we determined included mean potassium, potassium variability (defined as the standard deviation of all potassium levels) and percentage of ICU time below and above the reference range (3.5 through 5.0 mmol/L). These metrics were determined for the first ICU day (early phase) and the subsequent ICU days (late phase; that is, day 2 to day 7). We also compared potassium metrics and in-hospital mortality before and after GRIP-II was implemented in 2006.

## RESULTS

Of all 22,347 ICU admissions, 10,451 (47%) patients were included. A total of 206,987 potassium measurements were performed in these patients. Potassium was regulated by GRIP-II in 4,664 (45%) patients. The overall in-hospital mortality was 22%. There was a U-shaped relationship between the potassium level and in-hospital mortality ($P < 0.001$). Moreover, potassium variability was independently associated with outcome.

After implementation of GRIP-II, in the late phase the time below 3.5 mmol/l decreased from 9.2% to 3.9% and the time above 5.0 mmol/L decreased from 6.1% to 5.2%, and potassium variability decreased from 0.31 to 0.26 mmol/L (all $P < 0.001$). The overall decrease in hospital mortality from 23.3% before introduction of GRIP-II to 19.9% afterward ($P < 0.001$) was not related with a specific potassium subgroup.

## CONCLUSIONS

Hypokalemia, hyperkalemia and potassium variability were independently associated with increased mortality. Computerized potassium control clearly resulted in improved potassium metrics.

# INTRODUCTION

Potassium homeostasis is frequently disturbed in critically ill patients [1]. Underlying diseases or treatments in intensive care unit (ICU) patients often affect the $Na^+/K^+$-ATPase pump. This pump maintains the potassium gradient and can be influenced by many factors such as insulin, catecholamines and acid-base status. The long term potassium balance is regulated mainly by the kidney. Thus dyskalemia is often the result of renal impairment [1,2].

Both hypo- and hyperkalemia are known to induce potentially lethal arrhythmias and cardiac dysfunction, as well as other complications [1,3,4]. Derangements in serum potassium levels in ICU patients should therefore be avoided, and monitoring of potassium is mandatory.

There are surprisingly few data on the relationship between serum potassium and mortality in ICU patients. A recent study shows a strong, independent association between hyperkalemia at the onset of ICU treatment and in-hospital mortality, even at moderate increases above the normal range. A causal relation could not be demonstrated [5].

Our first objective in the present study was to evaluate the relationship between potassium levels and in-hospital mortality. In 2006, our ICU introduced a nurse-centered, computerized, potassium regulation protocol, integrated with previously implemented computerized glucose control. Our secondary objective was to evaluate the impact of this computerized protocol on potassium control.

# MATERIALS AND METHODS

## STUDY POPULATION

This retrospective observational cohort study was performed at the adult ICU of our university teaching hospital. This ICU includes three surgical subunits (including cardiothoracic surgery and neurosurgery) and a medical subunit, composing a total of 47 beds. All patients, ages >15 years who were admitted to the ICU during a 10-year period (2002 through 2011) were evaluated. In order to assess the role of ICU-acquired potassium derangements, only patients admitted for at least 24 hours were studied. If a patient had multiple ICU admissions, the first ICU admission of the patient's last hospital admission was used for analysis.

The anonymized data analysis in this study was performed in accordance with the guidelines and outlined in Dutch legislation, and the study was approved by the medical ethics committee of our institution (Medisch Ethische Commissie, UMC Groningen, METc 2014.264). Because this was a retrospective study of routinely collected data, informed consent was not required by our ethics committee.

**Table 1. Patient characteristics and blood summary statistics[a]**

| | Total (n=10,451) | Survivors (n=8,175) | Non-survivors (n=2,276) | *P* |
|---|---|---|---|---|
| **Baseline characteristics** | | | | |
| Age, yr, mean (SD) | 59.4 (16.7) | 58.3 (16.9) | 63.3 (15.4) | <0.001* |
| Sex, male, n(%) | 6,340 (60.7) | 5,007 (61.2) | 1,333 (58.6) | 0.021 |
| Reason of admission | | | | |
| Medical | 2,766 (27.5) | 1,798 (21.9) | 977 (42.9) | <0.001 |
| Surgical | 7,670 (73.5) | 6,372 (78.1) | 1,298 (57.1) | |
| Included in GRIP-II | 4,664 (44.6) | 3,735 (45.7) | 929 (40.8) | <0.001 |
| LOS ICU, days | 4.1 (2.0-10.1) | 3.8 (2.0-9.3) | 5.9 (2.9-12.8) | <0.001* |
| LOS hospital, days | 17.8 (10.1-32.0) | 19.8 (12.1-34.8) | 9.9 (4.2-21.4) | <0.001* |
| APACHE II score[b] | 16 (12-21) | 15 (11-19) | 21 (17-27) | <0.001* |
| AKI[c] | 3,443 (33.3) | 2,162 (26.5) | 1,281 (56.3) | <0.001 |
| Stage 1 | 1,388 (40.3) | 1,033 (47.8) | 355 (27.8) | |
| Stage 2 | 680 (19.8) | 432 (20.0) | 248 (19.4) | |
| Stage 3 | 1,375 (40.0) | 697 (31.8) | 678 (52.9) | |
| RRT | 999 (9.6) | 524 (6.4) | 475 (20.9) | <0.001 |
| **Potassium summary statistics, early phase[d]** | | | | |
| Admission $K^+$ level, mmol/L | 4.1 (3.7-4.5) | 4.0 (3.7-4.4) | 4.1 (3.7-4.7) | <0.001* |
| $K^+$ measurements, n | 6.0 (3.0-8.0) | 6.0 (3.0-8.0) | 5.0 (3.0-8.0) | 0.235* |
| Mean $K^+$ level, mmol/L | 4.2 (3.9-4.5) | 4.2 (3.9-4.5) | 4.2 (3.8-4.6) | 0.025* |
| $K^+$ variability, mmol/L | 0.29 (0.19-0.43) | 0.28 (0.19-0.42) | 0.32 (0.21-0.50) | <0.001* |
| $K^+$ range, mmol/L | 0.70 (0.40-1.10) | 0.70 (0.40-1.10) | 0.80 (0.40-1.20) | <0.001* |
| Time in hypokalemia, mean (SD)[e] | 7.4% (21.4) | 6.7% (20.7) | 9.8% (23,7) | <0.001* |
| Time in hyperkalemia, mean (SD)[e] | 7.6% (21.5) | 6.5% (19.7) | 11.4% (26.7) | <0.001* |
| Hypokalemia, mild | 1,877 (18.2%) | 1,417 (17.6%) | 460 (20.3%) | 0.003 |
| Hypokalemia, severe | 418 (4.0%) | 272 (3.4%) | 146 (6.5%) | <0.001 |
| Hyperkalemia, mild | 1,677 (16.2%) | 1,218 (15.1%) | 459 (20.3%) | <0.001 |
| Hyperkalemia, severe | 411 (4.0%) | 259 (3.2%) | 152 (6.7%) | <0.001 |
| **Potassium summary statistics, late phase** | | | | |
| Mean $K^+$ level, mmol/L | 4.2 (3.9-4.4) | 4.1 (3.9-4.4) | 4.2 (4.0-4.6) | <0.001* |
| $K^+$ measurements, n | 2.0 (1.0-3.9) | 1.9 (1.0-3.6) | 2.2 (1.1-4.5) | <0.001* |
| $K^+$ variability, mmol/L | 0.28 (0.19-0.40) | 0.26 (0.17-0.37) | 0.35 (0.24-0.51) | <0.001* |
| $K^+$ range, mmol/L | 0.28 (0.03-0.50) | 0.25 (0.00-0.47) | 0.36 (0.10-0.60) | <0.001* |
| Time in hypokalemia, mean (SD)[e] | 6.4% (17.6) | 6.3% (17.8) | 6.7% (16.8) | <0.001* |
| Time in hyperkalemia, mean (SD)[e] | 5.7% (17.0) | 3.5% (12.8) | 13.4% (25.9) | <0.001* |
| Hypokalemia, mild | 2,110 (20.2%) | 1,597 (19.5%) | 513 (22.5%) | 0.002 |
| Hypokalemia, severe | 345 (3.3%) | 237 (2.9%) | 108 (4.8%) | <0.001 |
| Hyperkalemia, mild | 1,733 (17.0%) | 1,127 (13.8%) | 646 (28.4%) | <0.001 |
| Hyperkalemia, severe | 375 (3.6%) | 140 (1.7%) | 235 (10.3%) | <0.001 |

[a]*GRIP-II*, Glucose and potassium regulation program for intensive care patients; *LOS*, Length of stay; *RRT*, Renal replacement therapy. Values are expressed as number (%) or median (interquartile range) unless otherwise specified. Statistical analysis was performed by using a $X^2$ test, unless marked by an asterisk, in which case a Mann-Whitney *U*-test was used.

[b]Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were available for 5,294 (50.7%) patients.

[c]Acute kidney injury (AKI) severity was defined by the Acute Kidney Injury Network's Kidney Disease: Improving Global Outcomes (KDIGO) criteria [8]. There were no data available for 6 (0.06%) patients.

[d]Potassium levels during the first 24 hours were known for 10,327 (98.8%) patients.

[e]Percentage of total intensive care unit (ICU) stay. Non-survivors and survivors differed significantly from each other. Non-survivors had more potassium derangements and a higher potassium variability.

## POTASSIUM MEASUREMENTS AND OTHER PARAMETERS

Potassium measurements determined before ICU admission, as well as samples known to be hemolyzed or otherwise obviously erroneous and thus considered as less reliable, were excluded. For this purpose, the authenticity of all potassium measurements ≥7.0 mmol/L and ≤2.0 mmol/L was also separately verified by examination of patient files. The selected measurements were verified by scanning the patients' medical record for known causes of extreme potassium serum levels, such as previously diagnosed hypo- or hyperkalemia, renal dysfunction and cardiopulmonary resuscitation during the corresponding hospital admission. When no plausible explanation was found for an extreme measurement and the measurement represented an isolated high or low value, preceded and followed by normal values from samples taken within 2 hours of the abnormal measurement, this measurement was excluded from further analysis.

Data was obtained from our electronic database and patient files and included basic demographics, reason for ICU admission, in-hospital mortality, inclusion in the glucose and potassium regulation program for intensive care patients (GRIP-II), and hospital follow-up. All potassium levels (reference range, 3.5 – 5.0 mmol/L), measured during the patient's ICU stay, with a maximum of the first 7 days of ICU-admission, were collected. A recent recommendation on glucose metrics was used as a guide to decide which potassium values to report [6]. Minimum, maximum and mean potassium levels, as well as potassium variability, were determined for every patient. The minimum and maximum potassium levels of the patient were used to derive the incidence of hypo- and hyperkalemia.

In cases where a patient was both hypokalemic and hyperkalemic, both values were counted. The potassium range was defined as the difference between the minimal and maximal potassium levels. Potassium variability was defined as the standard deviation (SD) of the potassium measurements in every patient. The admission serum potassium level was defined as the first measurement within 24 hours after ICU admission. Mild hypokalemia was defined as <3.5 mmol/L to 3.0 mmol/L, and severe hypokalemia was defined as <3.0 mmol/L.

Mild hyperkalemia was defined as >5.0 mmol/L to 6.0 mmol/L, and severe hyperkalemia was defined as >6.0 mmol/L [7]. Potassium levels were measured and recorded in millimoles per liter (1 mmol/L = 1 mEq/L).

Disturbances in renal function were defined and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition of acute kidney injury (AKI) [8]. Severity of illness was defined according to the Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, when available. Admission serum glucose was defined as the first glucose measurement within the first 24 hours after ICU admission. In order to assess the relation of marked admission hyperglycemia with potassium, hyperglycemia was categorized into 15 to 20 mmol/L and >20 mmol/L groups.

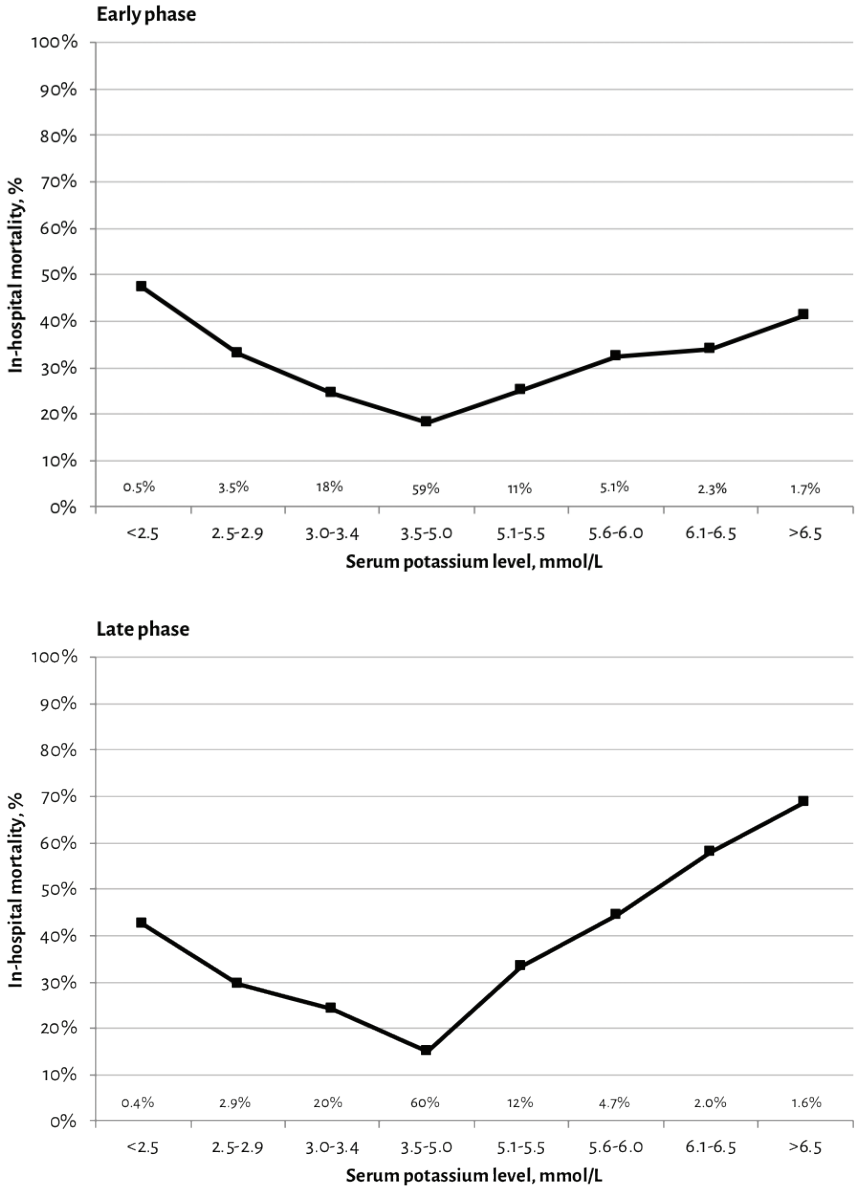


**Figure 1. Lowest and highest potassium levels and outcomes in the early and late phases of intensive care unit admission.**

Relationship between abnormal potassium levels and mortality during the first 24 hours of intensive care unit (ICU) admission (early phase; upper panel) and days 2 through 7 (late phase; lower panel) of ICU admission. This distinction was made because the initial derangements often cannot be influenced by ICU treatment. Both the lowest and the highest potassium levels measured during the relevant episode were used. Lower and higher potassium levels were both associated with a marked increase in mortality risk. The incidences are indicated above the x-axis. Thus, 59% and 60% of the patients had neither hypokalemia nor hyperkalemia in the early and late phases, respectively. Because some patients are represented in both a hypokalemic and a hyperkalemic category, the percentages add up to more than 100%.

## COMPUTERIZED POTASSIUM REGULATION PROTOCOL

A nurse-centered, computerized potassium regulation protocol called Glucose and potassium Regulation in Intensive Care Patients (GRIP) has been fully operational at our ICU for several years. This protocol was first implemented as a glucose regulation system (GRIP-I), but a potassium algorithm was successfully integrated later (GRIP-II). GRIP-II provides advice about the desired rate of potassium administration and the time interval until the next potassium measurement after analysis of a blood sample. All recommendations made by GRIP-II can be overruled or adjusted by a nurse or physician at any time, and all were automatically recorded. The potassium target range was set in the middle of the normal range (that is, 4.3 mmol/L), similar to the potassium target before implementation of this computerized protocol. More detailed descriptions of the design and implementation of this system have been published previously [9,10].

## ENDPOINTS

The primary endpoint of this study was in-hospital mortality. Secondary endpoint was the effect of GRIP-II on potassium control.

## STATISTICAL ANALYSIS

All potassium measurements were split into an early phase (first ICU day) and late phase (ICU day 2 through 7) for both the whole patient cohort and divided according to the regulation of GRIP-II. Baseline demographics and blood potassium levels were compared between survivors and non-survivors and before and after GRIP-II using contingency tables and the X2 test. The categorization of patients by regulation of serum potassium levels by GRIP-II was made by conducting an intention-to-treat analysis.

Logistic multivariate regression analysis was performed to assess the independent relationship between the obtained variables and in-hospital mortality. The regression analysis was corrected for sex, age, severity of illness, AKI, mean potassium, mean potassium squared and potassium variability. A two-sided *P* value of <0.05 was considered significant. Data reduction and statistical analysis were been performed with SPSS version 22 software (IBM SPSS, Chicago, IL, USA).

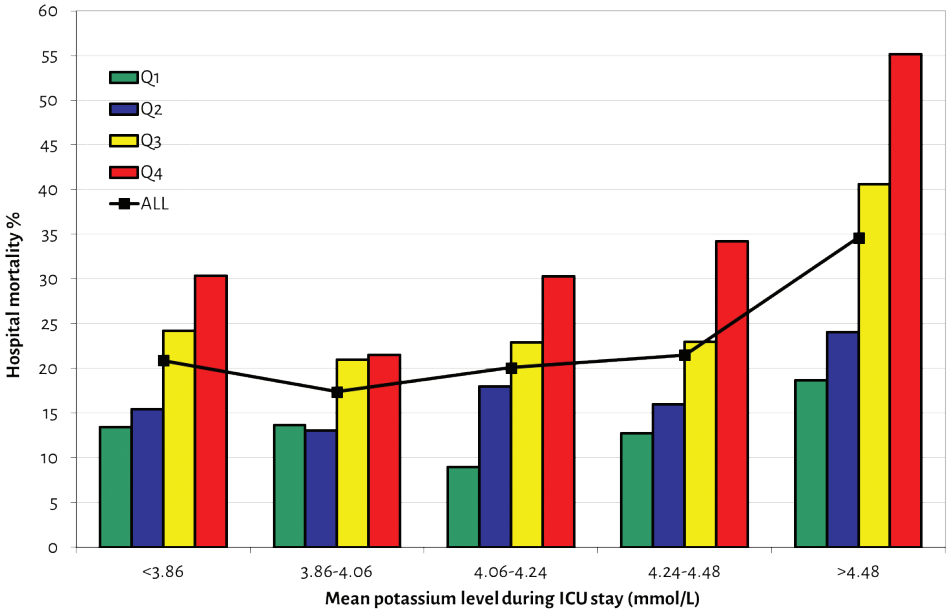


**Figure 2. Relationship of mean potassium level and potassium variability with mortality.**

The relationship between mean potassium and mortality is depicted for five quintiles (black curve). For each mean potassium quintile, quartiles of potassium variability (colored bars) are shown.

## RESULTS

During the study period, a total of 22,347 patients were admitted to our ICU, and they had a total of 256,410 serum potassium measurements. Of these potassium measurements, 256,200 (99.9%) were assessed as realistic. Eventually, we had 10,451 patients (46.7%) with an aggregate of 206,987 serum potassium measurements who were admitted to our ICU for more than 24 hours. The data gathered during the first 24 hours of ICU stay were available for 10,327 patients (98.8%). The minimum and maximum serum potassium levels observed were 1.5 mmol/L and 10.8 mmol/L respectively. The baseline characteristics of the 10,451 patients studied are shown in Table 1. AKI occurred in 3,443 (33.3%) of the patients. A total of 999 (9.6%) patients received renal replacement therapy (RRT).

### ABNORMAL SERUM POTASSIUM LEVELS AND IN-HOSPITAL MORTALITY

The in-hospital mortality number was 2,276 (21.8%) and admission potassium levels were higher in patients who died during their hospital stay than among patients who survived. It should be stressed that all the incidences mentioned refer to the number of patients with potassium derangements, not to the number of deranged measurements. There was a U-shaped relationship between potassium levels and in-hospital mortality ($P < 0.001$) (Figure 1). Potassium variability was independently related to outcome. The independent impact of variability is given in Figure 2, which shows mean potassium in quintiles and potassium variability in quartiles within each quintile (Table 2). Figure 2 shows evidence of lower in-hospital mortality associated with the lower normal range for potassium, as well as lower mortality associated with lower variability across all quintiles. Overall, we saw a lower potassium variability in survivors

in both the early and late phases ($P < 0.001$). The design of Figure 2 was copied as faithfully as possible from a figure reported by Krinsley [11] that depicted a very similar phenomenon for mean glucose and glucose variability. Multivariate analysis showed an independent association with in-hospital mortality for the occurrence of both hypokalemia and hyperkalemia and potassium variability with and without inclusion of APACHE-II and AKI data (Table 3).

**Table 2. Potassium variability quartiles used for each mean potassium quintile shown in Figure 2**

| Mean potassium concentration (mmol/L) | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
|---|---|---|---|---|
| <3.86 (n = 2,089) | <0.17 | 0.17 to 0.26 | 0.26 to 0.38 | >0.38 |
| 3.86 – 4.06 (n = 2,089) | <0.18 | 0.18 to 0.26 | 0.26 to 0.37 | >0.37 |
| 4.06 – 4.24 (n = 2,111) | <0.19 | 0.19 to 0.28 | 0.28 to 0.38 | >0.38 |
| 4.24 (4.48 (n = 2,080) | <0.19 | 0.19 to 0.28 | 0.28 to 0.40 | >0.40 |
| >4.48 (n = 2,082) | <0.21 | 0.21 to 0.33 | 0.33 to 0.51 | >0.51 |
| Total = 10,451 | | | | |

Time in hypo- and hyperkalemia was higher for nonsurvivors for both the early and late phases ($P < 0.001$) (Table 1). Time in hypo-and hyperkalemia was noted as a mean percentage of the total ICU stay not a median percentage, because the medians were 0%. Both mild and severe hypokalemia occurred more often in nonsurvivors than in survivors, during the early phase and the late phase. The incidence of mild and severe hyperkalemia was also higher in nonsurvivors.

## ABNORMAL SERUM POTASSIUM LEVELS AND IN-HOSPITAL MORTALITY BEFORE AND AFTER GRIP-II

A total of 4,664 (44.6%) patients were included in GRIP-II. The baseline patient characteristics before and after the introduction of GRIP-II are shown in Table 4. The mean ±SD ages before and after GRIP-II were 59 ±17 and 60 ±16 years, respectively, and 60% and 62% patients in these two groups, respectively, were male. After implementation of GRIP-II, the number of potassium measurements increased from 1.7 (interquartile range (IQR), 1.1 to 3.0) per patient per day to 5.5 (IQR, 3.5 to 7.3) measurements per patient per day ($P < 0.001$). The occurrence of AKI, as well the use of RRT, did not differ before and after the implementation of GRIP-II. More patients with AKI developed mild and severe hyperkalemia (Table 5). Also, patients with marked hyperglycemia at admission more frequently developed hyperkalemia than patients with normoglycemia (Table 6). The overall in-hospital mortality decreased from 1,347 (23.3%) to 929 (19.9%) after implementation of GRIP-II (Table 4). The U-shaped relationship between potassium extremes and mortality persisted after the introduction of GRIP-II (Figure 3).

Potassium variability was significantly less in patients regulated by GRIP-II during the late phase (Table 4), despite an increase of the potassium range after GRIP-II ($P < 0.001$). The time in hypo- and hyperkalemia was les in both phases for patients regulated by GRIP-II, but this improvement was particularly visible after 24 hours in survivors for the time in hypokalemia.

Late mild as well severe hypokalemia decreased in patients who were regulated by GRIP-II. Mild hyperkalemia, on the other hand, increased after implementation of GRIP-II. Severe hyperkalemia did not differ before and after implementation of GRIP-II.

## DISCUSSION

In this first study to comprehensively address the relationship of potassium concentration with outcome in the ICU, we show a strong relationship between potassium levels and potassium variability with in-hospital mortality, which persisted after adjustment for disease severity and AKI. After implementation of a novel computer-guided potassium algorithm, improvement of hypokalemia, hyperkalemia and potassium variability was observed.

The effect of our computerized regulation protocol was particularly visible during the late phase (that is, after the first 24 hours of ICU stay). This observation underscores the fact that GRIP-II cannot affect the potassium levels that patients have upon admission to the ICU, a time when abnormal laboratory values are particularly prevalent. Thus, GRIP-II required some time to correct abnormal levels.

Although the relationship of abnormal potassium levels and potassium variability with in-hospital mortality persisted, computerized control managed to get more patients within the normal range. For those patients who still had deranged potassium levels, the mortality rate was not higher after GRIP-II than before GRIP-II. Our present retrospective study, which covered a large period that saw important changes in critical care treatment, obviously does not allow to draw any definite conclusions on a potential beneficial mortality effect of GRIP-II, but at the least it suggests that stricter potassium control is feasible.

**Table 3. Multivariate analysis for hospital mortality[a]**

| | OR (95% CI) | *P* |
|---|---|---|
| **Model 1** | | |
| Sex, female | 1.08 (0.97 - 1.20) | 0.159 |
| Age | 1.018 (1.014 - 1.021) | <0.001 |
| Mean potassium | 0.002 (0.000 - | <0.001 |
| Mean potassium | 2.18 (1.85 - 2.57) | <0.001 |
| Potassium variability | 9.37 (7.25 - 12.10) | <0.001 |
| **Model 2** | | |
| Sex, female | 1.12 (1.01 – 1.25) | 0.032 |
| Age | 1.017 (1.013 – 1.020) | <0.001 |
| AKI | 2.50 (2.25 – 2.79) | <0.001 |
| Mean potassium | 0.003 (0.001 – 0.013) | <0.001 |
| Mean potassium | 2.02 (1.71 – 2.38) | <0.001 |
| Potassium variability | 5.83 (4.49 – 7.58) | <0.001 |
| **Model 3** | | |
| Sex, female | 1.22 (1.05 – 1.42) | 0.012 |
| Age | 1.008 (1.003 – 1.013) | 0.002 |
| APACHE-II | 1.104 (1.091 – 1.116) | <0.001 |
| AKI | 1.76 (1.50 – 2.06) | <0.001 |
| Mean potassium | 0.008 (0.001 – | <0.001 |
| Mean potassium | 1.84 (1.40 – 2.41) | <0.001 |
| Potassium variability | 5.61 (3.64 – 8.66) | <0.001 |

[a]CI, Confidence interval; OR, Odds ratio.

Data are adjusted for sex, age, acute kidney injury (AKI), severity of illness (Acute Physiology and Chronic Health Evaluation II (APACHE II) score), mean potassium, mean potassium squared and potassium variability as observed between 24 hours and 7 days after admission. For all variables except potassium variability (9,228 patients (88%)) and APACHE II score (4,883 patients (51%)), virtually complete data were available, therefore the multivariate analysis was performed with APACHE II score (lower panel) and without APACHE II score. In-hospital mortality was associated with all domains of potassium control. In order to test for a U-shaped relationship of mean potassium with hospital mortality, the mean potassium concentration was both included directly and squared.

In contrast to large recent observational study on the relationship between potassium and outcome [5], we took into account both sides of potassium derangements, finding an increased mortality rate in both hypo- and hyperkalemia. Hypo- and hyperkalemia are associated with an increased risk of potentially fatal complications. Both either should be avoided in critically ill patients or should be rapidly corrected when severely deranged [1-4,7]. The precise mechanisms that relate in-hospital mortality and potassium are not known. It has been proposed that mild abnormalities could be a marker of disease, whereas severe potassium derangements could be a cause of mortality [5]. Mild hypo- and hyperkalemia are often asymptomatic. Cardiac dysfunction is frequently caused by worse abnormalities.

**Table 4. Baseline characteristics and blood potassium summary statistics before and after introduction of GRIP-II[a]**

| | Before GRIP-II | | | | After GRIP-II | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total (n=5,787) | Survivors (n=4,440) | Non-survivors (n=1,347) | *P* | Total (n=4,664) | Survivors (n=3,735) | Non-survivors (n=929) | *P* | *P*[b] |
| **Baseline characteristics** | | | | | | | | | |
| Age, y, mean SD | 58.6 (17.1) | 57.3 (17.3) | 62.6 (15.7) | <0.001* | 60.4 (16.2) | 59.4 (16.4) | 64.2 (14.8) | <0.001* | <0.001 |
| Sex, male | 3453 (59.7) | 2652 (59.7) | 801 (59.5) | 0.863 | 2887 (61.9) | 2355 (63.1) | 532 (57.3) | 0.001 | 0.020 |
| Reason of admission | | | | | | | | | |
| Medical | 1979 (34.3) | 1270 (28.7) | 709 (52.6) | <0.001 | 787 (16.9) | 519 (13.9) | 268 (28.9) | <0.001 | <0.001 |
| Surgical | 3799 (65.7) | 3161 (71.3) | 638 (47.4) | <0.001 | 3871 (83.1) | 3211 (86.1) | 660 (71.1) | <0.001 | <0.001 |
| LOS ICU,d | 4.2 (21.-10.0) | 3.9 (2.0-9.0) | 5.8 (2.9-12.3) | <0.001* | 4.0 (2.0-10.5) | 3.8 (1.9-9.7) | 6.1 (3.0-13.4) | <0.001* | 0.194* |
| LOS hospital, d | 17.5 (9.9-18.3) | 19.8 (12.1-35.1) | 9.3 (4.1-20.1) | <0.001* | 18.1 (10.3-32.5) | 19.8 (12.2-34.5) | 10.3 (4.3-23.7) | <0.001* | 0.005* |
| APACHE-II[c] | 17 (12-22) | 15 (11-20) | 21 (17-28) | <0.001* | 16 (12-21) | 15 (11-19) | 21 (17-27) | <0.001* | 0.222* |
| AKI[d] | 1934 (33.4) | 1174 (26.5) | 760 (56.4) | <0.001 | 1509 (32.3) | 988 (26.4) | 521 (56.1) | <0.001 | 0.384 |
| Stage 1 | 767 (39.7) | 551 (47.0) | 216 (28.4) | | 621 (41.2) | 482 (48.8) | 139 (26.7) | | |
| Stage 2 | 376 (19.4) | 229 (19.5) | 147 (19.3) | | 304 (20.1) | 203 (20.5) | 101 (19.4) | | |
| Stage 3 | 791 (40.9) | 394 (33.5) | 397 (52.2) | | 584 (38.7) | 303 (30.7) | 281 (53.9) | | |
| RRT | 564 (9.7) | 299 (6.7) | 265 (19.7) | <0.001 | 435 (9.3) | 225 (6.0) | 210 (22.6) | <0.001 | 0.466 |
| Nr. of $K^+$ measurements/day | 1.7 (1.1-3.0) | 1.7 (1.1-3.1) | 1.6 (1.0-2.8) | 0.003* | 5.5 (3.5-7.3) | 5.4 (3.6-7.2) | 5.6 (3.0-8.1) | 0.032* | <0.001* |
| **Potassium summary statistics, early phase[e]** | | | | | | | | | |
| Admission $K^+$ level,mmol/L | 4.1 (3.7-4.5) | 4.1 (3.7-4.5) | 4.2 (3.7-4.7) | <0.001* | 4.0 (3.7-4.4) | 4.0 (3.7-4.4) | 4.1 (3.7-4.6) | 0.001* | <0.001* |
| Mean $K^+$ level, mmol/L | 4.1 (3.8-4.5) | 4.1 (3.8-4.5) | 4.2 (3.8-4.7) | <0.004* | 4.2 (3.9-4.5) | 4.2 (3.9-4.4) | 4.2 (3.8-4.5) | 0.935* | 0.007* |
| $K^+$ variability, mmol/L | 0.30 (0.17-0.47) | 0.29 (0.16-0.45) | 0.33 (0.18-0.53) | <0.001* | 0.29 (0.20-0.40) | 0.28 (0.19-0.39) | 0.32 (0.22-0.45) | <0.001* | 0.105* |
| $K^+$ range, mmol/L | 0.50 (0.20-1.00) | 0.5 (0.20-0.90) | 0.6 (0.30-1.1) | <0.001* | 0.80 (0.60-1.20) | 0.8 (0.60-1.20) | 0.9 (0.70-1.40) | <0.001* | <0.001* |
| Time in hypokalemia, mean SD[f] | 8.9 (25.3) | 8.2 (24.6) | 11.0 (25.3) | <0.001* | 5.5 (15.0) | 4.9 (14.4) | 8.0 (16.9) | <0.001* | <0.001* |
| Time in hyperkalemia, mean SD[f] | 8.1 (23.3) | 6.8 (21.3) | 12.0 (28.5) | <0.001* | 7.0 (19.0) | 6.1 (17.6) | 10.5 (23.8) | <0.001* | <0.001* |
| Hypokalemia, mild | 964 (16.9%) | 772 (16.5%) | 242 (18.0%) | 0.201 | 913 (19.8%) | 695 (18.8%) | 218 (23.7%) | 0.001 | <0.001 |
| Hypokalemia, severe | 226 (4.0%) | 147 (3.4%) | 79 (5.9%) | <0.001 | 192 (4.2%) | 125 (3.4%) | 67 (7.3%) | <0.001 | 0.590 |
| Hyperkalemia, mild | 850 (14.9%) | 612 (14.0%) | 238 (17.7%) | 0.001 | 827 (17.9%) | 606 (16.4%) | 221 (24.1%) | <0.001 | <0.001 |
| Hyperkalemia, severe | 227 (4.0%) | 128 (2.9%) | 99 (7.4%) | <0.001 | 184 (4.0%) | 131 (3.5%) | 53 (5.8%) | 0.002 | 0.961 |
| **Potassium summary statistics, late phase** | | | | | | | | | |
| Mean $K^+$ level, mmol/L | 4.1 (3.8-4.4) | 4.1 (3.8-4.3) | 4.2 (3.9-4.6) | <0.001* | 4.2 (4.0-4.4) | 4.2 (4.0-4.4) | 4.3 (4.1-4.6) | <0.001* | <0.001* |
| $K^+$ variability, mmol/L | 0.31 (0.20-0.46) | 0.29 (0.19-0.42) | 0.38 (0.25-0.55) | <0.001* | 0.26 (0.18-0.35) | 0.24 (0.17-0.32) | 0.33 (0.23-0.44) | <0.001* | <0.001* |
| Time in hypokalemia, mean SD[f] | 9.2 (20.9) | 9.1 (21.4) | 9.3 (19.4) | <0.001* | 3.0 (11.3) | 3.0 (11.4) | 3.0 (10.7) | 0.060* | <0.001* |
| Time in hyperkalemia, mean SD[f] | 6.1 (18.2) | 3.7 (13.6) | 13.9 (27.2) | <0.001* | 5.2 (15.5) | 2.2 (11.8) | 12.7 (23.9) | <0.001* | <0.001* |
| Hypokalemia, mild | 1346 (23.3%) | 998 (22.5%) | 348 (25.8%) | 0.011 | 764 (16.4%) | 599 (16.0%) | 165 (17.8%) | 0.204 | <0.001 |
| Hypokalemia, severe | 241 (4.2%) | 162 (3.6%) | 79 (5.9%) | <0.001 | 104 (2.2%) | 75 (2.0%) | 29 (3.2%) | 0.040 | <0.001 |
| Hyperkalemia, mild | 867 (15.0%) | 541 (12.2%) | 326 (24.2%) | <0.001 | 906 (19.4%) | 586 (15.7%) | 320 (34.4%) | <0.001 | <0.001 |
| Hyperkalemia, severe | 207 (3.6%) | 72 (1.7%) | 135 (10.0%) | <0.001 | 168 (3.6%) | 68 (1.8%) | 100 (10.7%) | <0.001 | 0.945 |

[a]*LOS*, Length of stay; *RRT*, Renal replacement therapy.

Data are expressed as number (%) or median (interquartile range) unless otherwise specified. Statistical analysis was performed by using a $\chi 2$ test, unless marked by an asterisk, in which case a Mann–Whitney *U*-test was used.

[b]Before and after glucose and potassium regulation program for intensive care patients (GRIP-II) comparison.

[c]Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were known for 5,294 (50.7%) patients.

[d]Acute kidney injury (AKI) was defined according to the Acute Kidney Injury Network's Kidney Disease: Improving Global Outcomes (KDIGO) criteria. There were no data available for six (0.06%) patients.

[e]Potassium levels during the first 24 hours were known for 10,327 (98.8%) patients.

[f]Percentage of total intensive care unit (ICU) stay.

That the multivariate relationships of both mean potassium and potassium variability with mortality (Figure 2, Table 2) was as marked as those observed by others for glucose [11] could be explained in at least two ways. One explanation could be that potassium variability has a direct causal relationship with outcome, such as through rapidly changing conditions in the cell membrane. A second explanation could be that a higher potassium variability, or, for that matter, variability of many other parameters, may be marker of patient instability in general. Recently it was reported that fluctuations in sodium were also associated with outcome [12]. Until more mechanistic data are available, we believe the second, noncausal explanation is more appropriate. Regardless of whether it may be useful, the GRIP-system was able to decrease potassium variability.

**Table 5. Relation between admission hyperkalemia and AKI before and after GRIP-II**

| | Before GRIP-II | | | | After GRIP-II | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total (n=5,714) | no AKI (n=3,798) | AKI (n=1,925) | *P* | Total (n=4,609) | no AKI (n=3,110) | AKI (n=1,499) | *P* | *P*[a] |
| Normokalemia | 4,637 (81.2) | 3,330 (87.9) | 1,307 (67.9) | <0.001 | 3,598 (78.1) | 2,691 (86.5) | 907 (60.5) | <0.001 | <0.001 |
| Hyperkalemia, mild | 850 (14.9) | 405 (10.7) | 445 (23.1) | <0.001 | 827 (17.9) | 367 (11.8) | 460 (30.7) | <0.001 | 0.098 |
| Hyperkalemia, severe | 227 (4.0) | 54 (1.4) | 173 (9.0) | <0.001 | 184 (4.0) | 52 (1.7) | 132 (8.8) | <0.001 | 0.179 |

Numbers are expressed as numbers (%) unless otherwise specified. Statistical analysis was performed by using a Chi Square test.

[a]Before and after GRIP-II compared.

Integration of GRIP-II into our ICU workflow was well accepted by both nurses and physicians. Because potassium regulation was integrated into an already existent glucose-control protocol, it did not add any significant nursing time or costs [10]. We consider it as a good example of noncritical tasks being successfully delegated to nurses and being computerized. To our knowledge, no other ICUs have yet incorporated GRIP-II, despite its being freely available on the internet. GRIP-II currently operates independent of a Patient Data Management System (PDMS), but the algorithm can also be incorporated into a PDMS. Despite safely reducing the number of patients with hypokalemia and reducing time in hypokalemia and time in hyperkalemia, GRIP-II caused a mild increase in moderate hyperkalemia. Preventing hyperkalemia and hypokalemia through GRIP-II was achieved only by regulating potassium infusion, because other actions to change potassium levels could be prescribed only by the intensivist. Thus, in cases of (impending) hyperkalemia, GRIP-II can only discontinue the potassium infusion. We assumed that this mechanism caused a higher incidence of patients with mild hyperkalemia post-GRIP, although the time in hyperkalemia decreased (Table 4). On the basis of these results, we have recently adjusted the GRIP-II target downwards slightly, from 4.3 mmol/L (in the middle of the 3.5 to 5.0 reference range) to 4.0 mmol/L

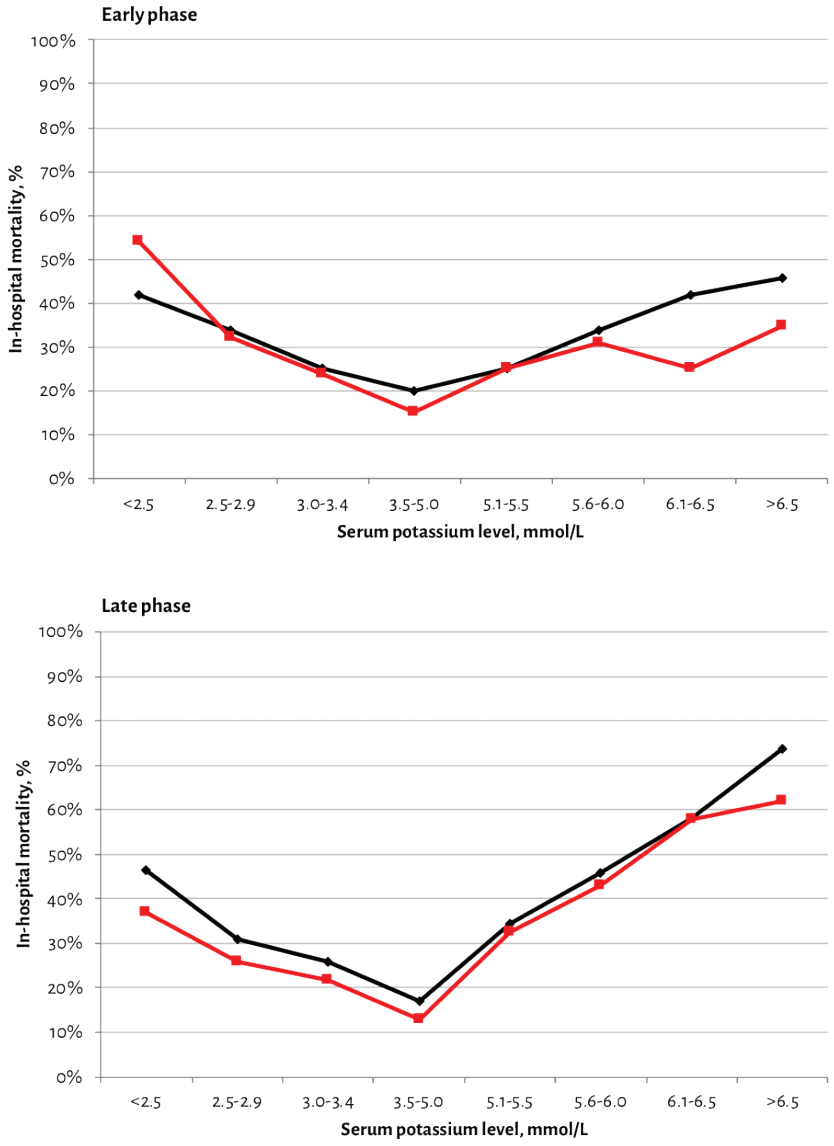


**Figure 3. Relationship between lowest and highest potassium level and outcome during before and after glucose and potassium regulation program for intensive care patients (GRIP-II).**

Analogously to Figure 1, here mortality is depicted as a function of abnormal potassium values observed during the early phase (upper panel) and the late phase (lower panel). Patients treated before GRIP-II are shown in black and with GRIP-II in red. Note that, in contrast to the early phase, mortality in the late phase is either comparable or lower in the GRIP-II group across the potassium range.

The precise optimal range for desired potassium levels remains unknown. This has been studied in different patient cohorts, varying between 3.5 and 4.5 mmol/L [13], 4.0 and 5.0 mmol/L [14], or even 4.5 and 5.5 mmol/L in acute myocardial infarction and HF patients [15], with no consensus reached. Currently, 3.5 to 5.0 mmol/L is accepted as a safe range for ICU patients. Whether cut-off points for potassium should be more precise and could affect outcome is still unclear.
If deemed sufficiently relevant, a large prospective trial would be required to address these unanswered questions. For example, the researchers in the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, investigated glucose control in a multicenter trial with over with over 6,000 patients [16].

Our study has several important limitations. A key limitation of our study is its retrospective design, so any conclusions regarding a causal effect of GRIP-II on outcome would be inappropriate. The before-after design introduces many forms of bias, in particular because many aspects of critical care have changed over the observation period, as underscored by the differences in baseline characteristics. The greatest before-after difference was the greater number of potassium measurements in patients controlled by GRIP-II, which will have affected metrics. But irrespective of the before-after character of our study, the obvious impact of close potassium monitoring by GRIP-II on the quality of regulation itself cannot be denied. We think that a potential future randomized study will be appropriate only when two computer-guided protocols are compared, as in our GRIP-COMPASS study [17], in which we compared the effect of two different computer-guided targets on atrial fibrillation after cardiac surgery. Our potassium metrics were derived from studies on glycemic control. We considered only potassium, sex, age, severity of illness, renal function, hyperglycemia and in-hospital mortality. We also did not have APACHE II scores for an important early part of the cohort. Likewise, we did not have the access to trustworthy data about the use of drugs that could influence potassium regulation. Therefore, we were not able to take these factors into consideration.

**Table 6. Relation between hyperkalemia and admission hyperglycemia before and after GRIP-II**

| | **Before GRIP-II** | | | | **After GRIP-II** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Total (n=5,714)** | **no AKI (n=3,798)** | **AKI (n=1,925)** | ***P*** | **Total (n=4,609)** | **no AKI (n=3,110)** | **AKI (n=1,499)** | ***P*** | ***P*** [a] |
| Normokalemia | 4,637 (81.2) | 3,330 (87.9) | 1,307 (67.9) | <0.001 | 3,598 (78.1) | 2,691 (86.5) | 907 (60.5) | <0.001 | <0.001 |
| Hyperkalemia, mild | 850 (14.9) | 405 (10.7) | 445 (23.1) | <0.001 | 827 (17.9) | 367 (11.8) | 460 (30.7) | <0.001 | 0.098 |
| Hyperkalemia, severe | 227 (4.0) | 54 (1.4) | 173 (9.0) | <0.001 | 184 (4.0) | 52 (1.7) | 132 (8.8) | <0.001 | 0.179 |

Numbers are expressed as numbers (%) unless otherwise specified. Statistical analysis was performed by using a Chi Square test. Admission glucose levels were available for 10,275 (96.3) patients.

[a]Before and after GRIP-II compared.

## CONCLUSIONS

In a study unique for its scope and size, we found a clear U-shaped relationship between early and late potassium levels and outcome. Potassium variability had a statistically independent relationship with outcome. Whether a causal relationship of variability with outcome exists is questionable.

Implementation of GRIP-II led to a decrease in potassium derangements. More stringent potassium control and decreased potassium variability could influence outcome, although such an effect can be proven only in a large prospective study.

## ACKNOWLEDGEMENTS

We thank Ria Oosterbaan for invaluable administrative support.

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# CHAPTER 3

# COMPUTER-GUIDED NORMAL-LOW VERSUS NORMAL-HIGH POTASSIUM CONTROL AFTER CARDIAC SURGERY: NO IMPACT ON ATRIAL FIBRILLATION OR ATRIAL FLUTTER

**American Heart Journal**
**2016;172:45-52**

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# ABSTRACT

## INTRODUCTION

This study was designed to determine the effect of two different potassium regulation strategies with different targets (within the reference range) on atrial fibrillation (AF) or atrial flutter (AFL) in a cohort of intensive care unit (ICU) patients after cardiac surgery.

## METHODS

The GRIP-COMPASS study was a prospective double-blinded interventional study in 910 patients after cardiac surgery (coronary artery bypass grafting and/or valvular surgery). Patients were assigned to either the normal-low potassium target (nLP group, 4.0 mmol/L) or the normal-high potassium target (nHP group, 4.5 mmol/L) in alternating blocks of 50 patients. Potassium levels were regulated using a validated computer-assisted potassium replacement protocol (GRIP-II). The primary end point was the incidence of AF/AFL on a 12-lead ECG during the first postoperative week.

## RESULTS

Of the 910 patients, 447 were assigned to the nLP group and 463 to the nHP group, with no baseline differences between the two groups. The mean ±SD daily administered dose of potassium was 30 ±23 mmol (nLP) versus 52 ±27 mmol (nHP) ($P < 0.001$), which resulted in a mean ICU potassium concentration of respectively 4.22 ±0.36 mmol/L and 4.33 ±0.34 mmol/L, respectively ($P < 0.001$). The incidence of AF/ AFL after cardiac surgery did not differ: 38% in the nLP group and 41% in the nHP group. Also in several subgroups (e.g. patients not known with prior AF/AFL or with valve surgery), there were no differences.

## CONCLUSIONS

There were no differences in incidence of AF/AFL with two potassium regulation strategies with different potassium targets and different amounts of potassium administered in patients after cardiac surgery.

# INTRODUCTION

Atrial fibrillation (AF) or atrial flutter (AFL) occurs frequently in patients admitted to the intensive care unit (ICU) after cardiac surgery and is associated with increased morbidity and mortality [1,2]. The underlying mechanisms are multifactorial and can be divided into patient-related factors (structural heart disease, older age) and acute surgery-related factors (mitral valve surgery, cardiopulmonary bypass). Adrenergic activation related to surgical stress and inflammation plays an important role [3, 4]. Another possible risk factor for the development for AF/AFL could be potassium derangements because they are associated with supraventricular arrhythmia [4, 5, 6].

Whether tight potassium regulation could reduce the incidence of postoperative AF/AFL is unknown. In a general cardiovascular population, a normal-high potassium level is associated with positive outcome [7]. We hypothesized that a normal-high potassium target during ICU admission might also be beneficial in the prevention of postoperative AF and AFL after cardiac surgery [7,8]. In the present single center, prospectively controlled trial, we compared a computer-guided normal-low potassium control strategy with a normal-high potassium control strategy on the occurrence of AF/AFL in patients after cardiac surgery.

# METHODS

## STUDY DESIGN

The computer-driven Glucose and potassium Regulation program in Intensive care Patients with COMparison of PotASSium targets within normokalemic range (GRIP-COMPASS) trial was a prospective double-blinded interventional study comparing two potassium control strategies and the effect on AF and AFL after cardiac surgery. Inclusion started June 2009 and ended October 2010. The study design has been described previously [8]. Study approval was obtained from the institutional medical ethics committee (METc 2009/096) and the study protocol was registered at ClinicalTrials.gov (NCT 01085071). Informed consent was waived by the institutional medical ethics committee because in both study arms, the potassium regulation protocol is standard care in our institution, with the only difference that the two arms aimed at two specific levels that were both within the reference range instead of just any level within the reference range. No extramural funding was used to support this work.

The study was performed in a 13-bed cardiothoracic ICU in the Netherlands that is part of a larger 45-bed adult ICU of the University Medical Center Groningen. All adult patients admitted during the study period were considered eligible for inclusion. Inclusion criteria was admission after cardiac surgery (coronary artery bypass grafting [CABG] and/or valve surgery). Exclusion criteria were the absence of a central venous line or an enteral feeding tube, as those were mandatory for the computer-assisted potassium control as performed by GRIP-II (Glucose and potassium Regulation in Intensive care Patients) in this institution. After inclusion, the patients were allocated to the normal-low potassium (nLP) target (4.0 mmol/L) or normal-high potassium (nHP) target (4.5 mmol/L) in alternating blocks of 50 consecutive patients. Patients remained in this treatment strategy until ICU discharge.

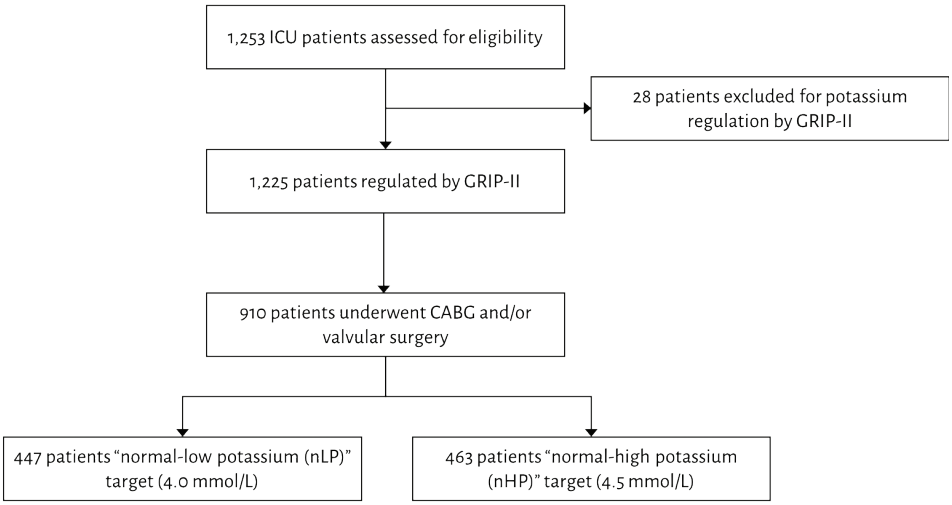


**Figure 1. Flowchart of the GRIP-COMPASS study.**

At ICU admission, patients after cardiac surgery were assigned to either the nLP or nHP in blocks of 50 patients.

## COMPUTER-ASSISTED POTASSIUM REGULATION

After inclusion immediately following ICU admission, potassium was regulated according to the allocated potassium target of 4.0 mmol/L or 4.5 mmol/L, by the computer-assisted potassium regulation protocol called GRIP-II [9-11]. The physicians, nurses and patients were unaware for the allocated treatment strategy. GRIP-II is a nurse-based integrated potassium and glucose regulation program that periodically provides advices on the desired potassium and insulin infusion rates as well as the next sampling time. Potassium is administered continuously by a syringe pump in a 1 mmol/ml concentration over a central venous catheter or enterally over a gastric, duodenal or jejunal tube. For the potassium algorithm, the advised pump rate is based on both the potassium trend over time and specific patient characteristics such as kidney function. In addition to the regulation algorithm, it also acts as a warning system for out-of-range potassium and glucose levels. Blood samples for potassium measurements were taken from the arterial line in lithium-heparin anti-coagulated syringes (PICO, Radiometer, Copenhagen, Denmark) and analyzed by a point-of-care (POC) blood gas analyzer present at the ICU (ABL Radiometer 800 series, Radiometer, Copenhagen). After ICU discharge potassium regulation was physician-based, without the help of a specific algorithm and also without a specific target. During ICU admission the standard infusion fluid for the basal daily requirement was saline 0.45% with glucose 2.5%. Cardiac patients were started on continuous magnesium sulfate supplementation of 30 mmol/d upon arrival at the ICU.

## STUDY END POINTS

Primary end point was the incidence of AF/AFL in the first 7 days after cardiac surgery (CABG and or valve surgery) with or without the use of cardiopulmonary bypass. The presence of AF/AFL had to be confirmed with a 12-lead electrocardiogram (ECG), with the arrhythmia present for the entire registration (10 seconds). Secondary end points were the level of potassium control (mean potassium values, mean daily amount of administered potassium, incidence of hypokalemia and hyperkalemia). Tertiary end points were length of stay (ICU and hospital), acute myocardial infarction, cerebral vascular accidents (CVA), kidney failure requiring renal replacement therapy, and mortality (at ICU, hospital, 90 days, and one-year).

## DATA COLLECTION

Patient demographics were collected at ICU admission. In addition, for patients admitted after cardiac surgery, data regarding the intraoperative period were retrieved from the anesthetic report. A case report form (CRF) was filled out for every included patient and collected at hospital discharge. All medical procedures, including computerized potassium control, ECG monitoring and laboratory measurements were part of routine clinical care. All laboratory data was retrieved from the hospital information system. Data regarding potassium and glucose control were retrieved from the GRIP-II electronic database. The EuroSCORE II model and the Acute Physiology and Chronic Health Evaluation II score were used to calculate the mortality risk in patients undergoing cardiac surgery [12,13]. Long-term mortality follow-up was performed through coupling of municipal mortality records with complete follow-up for 3 years. All patient data were managed anonymously.

A 12-lead ECG was made at ICU admission, daily for the first 5 ICU days, at hospital discharge, when a rhythm disorder was observed on the monitor, or when the patient was having complaints. During ICU admission, all patients were monitored continuously with a 12-lead ECG with rhythm recognition and ST segment monitoring. When a patient was considered at risk to develop severe arrhythmias, continuous monitoring by telemetry was continued at the general ward. For the primary end point, the occurrence of AF/AFL was defined as AF or AFL confirmed by a stored 12-lead ECG (during the entire 10 seconds of registration), reviewed by an independent and qualified cardiologist, blinded for the treatment allocation. Patients who developed AF/AFL were treated according to local guidelines (magnesium >0.80 mmol/L, amiodarone, and β-blockers). Anticoagulation was started when AF/AFL was present for over 24 hours. All patients who died during hospital admission were closely reviewed if abnormal potassium levels could have attributed to the cause of death.

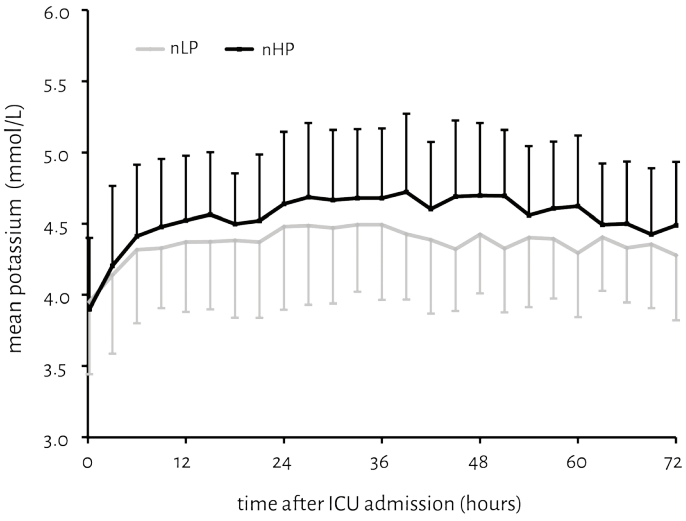


**Figure 2. Potassium concentration during the first 72 hours after ICU admission.**
This figure demonstrates the mean potassium concentration after ICU admission during 72 hours for both the nLP and nHP groups.

## STATISTICAL ANALYSIS

For the primary endpoint, a power analysis was performed based on a previous 3-month observation in our institution that of the patients after cardiac surgery approximately 50% developed AF/AFL during hospital admission. With a 2-sided level of significance of 5% and a power of 80%, 800 cardiac surgery patients should be included to detect a 10% reduction in the incidence of AF/AFL. As indicated before, all patients admitted to the ICU received potassium control with GRIP-II. Assuming that approximately 75% of the admitted patients would undergo cardiac surgery and (with a 10% margin), we arrived at a target number of 1200 consecutive patients.

To compare groups, the Student *t*-test, the Mann-Whitney *U*-test or Fisher exact test was used when appropriate. Secondary analyses were performed in predefined subgroups [8]. A log-rank test was used to compare Kaplan-Meier curves. Multivariate analyses were performed to determine predictors for postoperative AF/AFL in cardiac surgery. A two-sided *P* value <0.05 was considered significant. All data was analysed using the intention to treat principle. SPSS version 20.0 was used for all statistical analyses.

The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript

## RESULTS

During the study period,1,253 consecutive patients were considered eligible. Of those patients, 28 were excluded based on the exclusion criteria (Figure 1). Of the remaining patients, 910 patients were admitted after cardiac surgery. Those patients were allocated to either the nLP or nHP potassium treatment strategy. For this group, the mean ±SD age was 66 ±13 years, and 67% was male. Most patients were admitted after valve surgery or off-pump CABG. A total of 447 patients were allocated to the nLP group, and 463 patients were allocated to the nHP group. Demographic, baseline, and intraoperative patient characteristics are demonstrated in Table 1. There were no statistical differences in baseline characteristics between the two groups.

During ICU admission, the mean amount of administered potassium was 30 ±23 mmol/day for the nLP group and 52 ±27 mmol/d for the nHP group ($P < 0.001$, Table 2). This resulted in mean ICU potassium concentration of 4.22 ±0.36 mmol/L and 4.33 ±0.34 mmol/L, respectively ($P < 0.001$). See Figures 2 and 3 for the trends over time in potassium administration and potassium values during ICU admission. After admission, the mean potassium values start to differ after 6 hours. There was no difference in the occurrence of severe hypokalemia and hyperkalemia (<2.5 mmol/L and >6.5 mmol/L) between the two groups (Table 2).

Mean magnesium levels during ICU stay were equal for both groups (nLP 1.04 ±0.18 and nHP 1.04 ±0.22).

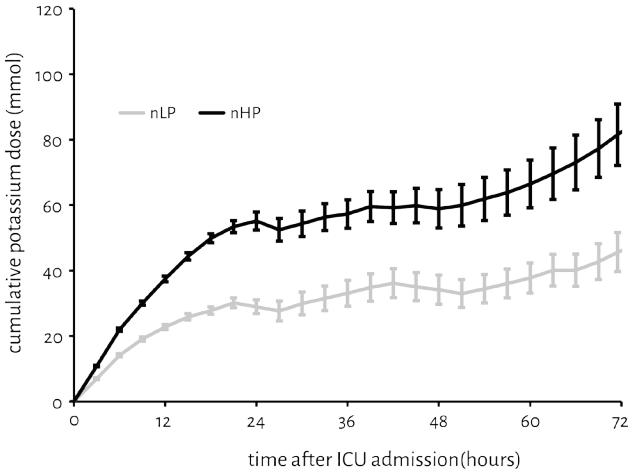


**Figure 3. Potassium administration during ICU admission.**

This figure demonstrates the cumulative amount of potassium administered for both the nLP and nHP group during the first 72 hours after ICU admission.

**Table 1. Demographics and clinical and surgical characteristics**

| Characteristics | nLP group n = 447 | nHP group n = 463 |
|---|---|---|
| Age, mean ±SD, y | 66 ±12 | 66 ±13 |
| Male | 300 (67) | 311 (67) |
| Body mass index, mean ±SD, kg/m2 | 27 ±4 | 27 ±4 |
| History of: | | |
| Hypertension | 190 (43) | 199 (43) |
| Diabetes mellitus, non insulin dependent | 59 (13) | 75 (16) |
| Diabetes mellitus, insulin dependent | 40 (9) | 30 (6) |
| Pulmonary disease | 53 (12) | 56 (12) |
| Chronic renal dysfunction | 40 (9) | 37 (8) |
| Atrial fibrillation and/or atrial flutter | 85 (19) | 82 (18) |
| Cerebrovascular accident | 48 (11) | 55 (12) |
| Cardiac status (left ventricular function)[a] | | |
| Moderate | 91 (20) | 86 (19) |
| Poor | 70 (16) | 77 (17) |
| Kidney function | | |
| Normal (eGFR[b]>90 mL/min) | 171/445 (38) | 153/460 (33) |
| Mildly reduced (eGFR 60-89 mL/min) | 192/445 (43) | 210/460 (46) |
| Moderately reduced (eGFR 30-59 mL/min) | 68/445 (15) | 84/460 (18) |
| Severely reduced (eGFR 15-29 mL/min) | 11/445 (3) | 8/460 (2) |
| End-stage kidney failure (eGFR <15 or on dialysis) | 3/445 (1) | 5/460 (1) |
| Prehospital medication | | |
| β-blockers | 283/424 (67) | 295/428 (69) |
| ACE inhibitor | 158/416 (38) | 159/422 (38) |
| ATII receptor blockers | 48/414 (12) | 47/419 (11) |
| Diuretics | 159/415 (38) | 151/423 (36) |
| Statins | 258/417 (62) | 247/421 (59) |
| Potassium-sparing diuretics | 33/413 (8) | 32/419 (8) |
| Digoxine | 13/413 (3) | 14/419 (3) |
| Other antiarrhythmic agents | 34/316 (8) | 24/419 (6) |
| EuroScore-II, mean ±SD | 3.5 ±6.0 | 3.2 ±4.8 |
| APACHE-II, mean ±SD | 43 ±17 | 44 ±17 |
| Recent myocardial infarction (<90 days) | 87 (19) | 76 (16) |
| Type of surgery: | | |
| Valve surgery | 157 (35) | 157 (34) |
| Single Aortic valve | 91 (20) | 103 (22) |
| Single Mitral valve | 30 (7) | 31 (7) |
| Combination / other | 36 (8) | 23 (5) |
| CABG (off-pump) | 147 (33) | 169 (37) |
| CABG (on-pump) | 65 (15) | 65 (14) |
| CABG plus valve | 78 (17) | 72 (16) |
| Repeat surgery | 26 (6) | 29 (6) |
| Duration of procedure, mean ±SD, min | 246 ±89 | 240 ±92 |
| Duration of extracorporeal circulation, mean ±SD, min | 153 ±71 | 149 ±75 |
| Duration of aortic cross-clamping, mean ±SD, min | 106 ±50 | 103 ±49 |

Data are presented as number (percentages) unless otherwise specified.

Abbreviations: e*GFR*, estimated glomerular filtration rate; *ACE*, angiotensin-converting enzyme; *ATII*, angiotensin II; *APACHE*, Acute Physiology and Chronic Health Evaluation.

[a] Moderate left ventricular function: ejection fraction 30-50%, poor left ventricular function: ejection fraction <30%.

[b] Estimated glomerular filtration rate, calculated using the modification of diet in renal disease equation.

For the primary end point, there was no statistical difference, as the incidence for AF/AFL after cardiac surgery was 172 (38%) for the nLP group and 188 (41%) for the nHP group. Kaplan-Meier time to event curves for the two groups were not different (Figure 4). Of the patients who developed AF/AFL, 75% presented within the first 3 days after surgery, with the highest incidence on the second day.

Also in several predefined groups (including patients without a history of AF/AFL) no differences were found for the primary end point (Figure 5). In the subgroup with a poor baseline renal function (estimated glomerular filtration rate <30 mL/min), there was no difference for the primary end point (31% vs. 33%). In multivariate analysis, independent predictors for postoperative AF or AFL were older age, prior AF/AFL and valve surgery ($P < 0.001$). Length of stay for the ICU and total hospitalization were comparable for the two groups (Table 2). There were no differences in inotrope requirements during the first 24 hours after surgery, except for the use of milrinone (Table 2). In addition, there were no statistically significant differences in the incidence of cerebral vascular accidents, acute myocardial infarction, the need for renal replacement therapy and mortality.

Patients who developed AF/AFL were more likely to develop a CVA (1.6% versus 5.8%, $P = 0.001$) or to die during hospitalization (2.9% versus 6.1%, $P = 0.03$). There were no in-hospital deaths that, in retrospective analysis, could be related to hypokalemic or hyperkalemic events as the cause of death.

## DISCUSSION

In this prospective trial on patients after open heart surgery, no difference was observed between two different potassium regulation strategies with a normal-low and normal-high potassium target for their effect on the incidence of AF/AFL.

The achieved potassium ranges for the nLP and nHP groups were closer to each other than the predefined targets, despite a markedly (+73%) higher potassium infusion rate in the nHP group. This proximity of the achieved nLP and nHP ranges was unexpected and possibly indicates an intrinsic tendency of potassium levels to settle near 4.2 mmol/L. With regard to the safety of GRIP-II algorithm, we observed very few extreme potassium derangements in both the target groups. This is in accordance with our experiences with the approximately 10,000 patients at our ICU that have been potassium managed by GRIP-II since 2006 [9,14].

**Table 2. Potassium regulation and outcome after cardiac surgery**

| | nLP group n= 447 | nHP group n=463 | *P* |
|---|---|---|---|
| Intensive care unit (ICU) | | | |
| Admission potassium, mmol/L (mean ±SD) | 3.96 ±0.49 | 3.97 ±0.51 | 0.70 |
| Potassium, mmol/L (mean ±SD) | 4.22 ±0.36 | 4.33 ±0.34 | <0.001 |
| Number of measurements | 8544 | 8957 | |
| Potassium administration, mmol/day (mean ±SD) | 30 ± 23 | 52 ± 27 | <0.001 |
| Severe hypokalemia (<2.5 mmol/L), no patients (%) | 2 (0.4) | 1 (0.2) | 0.62 |
| Severe hyperkalemia (>6.5 mmol/L), no patients (%) | 8 (1.8) | 16 (2.4) | 0.65 |
| After ICU discharge, at the general ward | | | |
| Potassium, mmol/L (mean ±SD) | 4.22 ±0.4 | 4.22 ±0.4 | 0.78 |
| Number of measurements | 3526 | 3470 | |
| Severe hypokalemia (<2.5 mmol/L), no patients (%) | 0/443 (0) | 3/453 (0.6) | 0.25 |
| Severe hyperkalemia (>6.5 mmol/L), no patients (%) | 3/443 (0.7) | 3/453 (0.6) | 1 |
| ICU Length of stay, median (IQR), days | 0.9 (0.8-1.1) | 0.9 (0.8-1.7) | 0.62 |
| Hospital length of stay, median (IQR), days | 10.1 (7.3-15.3) | 10.2 (7.3-15.3) | 0.36 |
| Myocardial infarction | 9 (2.0) | 3 (0.6) | 0.09 |
| Kidney failure (renal replacement therapy at ICU) | 8 (1.8) | 14 (3.0) | 0.28 |
| CVA | 14 (3.1) | 16 (3.5) | 0.85 |
| Transfusions | | | |
| Red blood cells, no patients (%) | 157 (35) | 159 (34) | 0.84 |
| Fresh frozen plasma, no patients (%) | 33 (7) | 30 (6) | 0.60 |
| Thrombocytes, no patients (%) | 35 (8) | 52 (11) | 0.09 |
| Inotrope use during the first 24 hours after surgery | | | |
| Noradrenaline | 161/420 (38) | 166/426 (39) | 0.88 |
| Dopamine | 181/420 (43) | 178/426 (42) | 0.73 |
| Dobutamine | 4/420 (1) | 10/426 (2) | 0.18 |
| Milrinone | 123/420 (29) | 99/426 (23) | 0.05 |
| Epinephrine | 7/420 (2) | 2/426 (0.5) | 0.10 |
| ICU mortality | 8 (1.8) | 15 (3.2) | 0.21 |
| Hospital mortality | 14 (3.1) | 25 (5.4) | 0.10 |
| 90-days mortality | 20 (4.5) | 32 (6.9) | 0,12 |
| One-year mortality | 25 (5.6) | 39 (8.4) | 0.12 |

Data are presented as number (percentages), unless otherwise specified.

Abbreviation: *IQR*, interquartile range.

Although potassium regulation at the ICU is considered important, few studies describe strategies to regulate potassium in the critically ill patient. Although in related patient groups abnormal potassium levels are associated with adverse outcome [15-17], to our knowledge, there are no studies comparing different potassium-based treatment strategies at the ICU and outcome. Potassium as part of a glucose-insulin-potassium regime was studied more extensively in acute myocardial infarction and during cardiac surgery [18].

Methodologically, we believe our trial contains two novel elements. First, it compared two target levels that both were within the physiological range. Second, the two underlying potassium infusion strategies (nLP and nHP) were implemented through computer support. The GRIP-potassium control system was able to effectively regulate potassium, indicating that integrated glucose and potassium control in the ICU is not only possible but useful as well. In the domain of glucose control, the comparison of two at least partially computer-guided protocols did demonstrate the superiority of a higher glucose target over a lower target [19]. Advanced control algorithms such as GRIP-II could also be applied to other parameters such as magnesium, calcium, or sodium that are difficult or time-consuming for humans to carefully regulate.

The two treatment strategies that we studied did not show different outcomes in terms of the incidence of AF/AFL. This may be the result of the targets being comparatively close, and the actually achieved levels even closer. Thus, it is conceivable that more separate potassium targets may produce different outcomes. As far as has been suggested by other authors, most studies pointed towards a protective effect of higher potassium levels in cardiovascular patients [7]. We found no differences in the incidence of AF/AFL, also not in the prespecified subgroups. Our results do not even indicate a trend towards a beneficial effect of higher potassium on AF/AFL.

Our study has important limitations. Although our trial was larger than most studies that compared the effect of interventions on AF or AFL [20], it may not have been sufficiently large to detect a difference. In addition, the incidence of AF/AFL was lower in the study population than the suspected incidence used for the power analysis. Likewise, our patients were not randomized one by one but were treated with an alternating target of low or high normal potassium. The data show that the nLP and nHP groups were well balanced at baseline, and we believe that the alternating target design did not introduce undue bias.

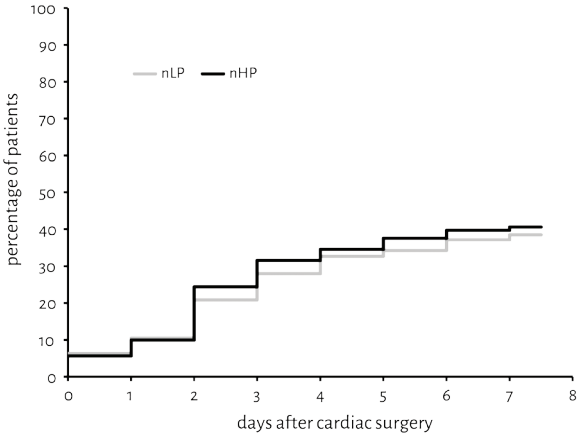


**Figure 4. Atrial fibrillation or atrial flutter after cardiac surgery.**

This figure shows the percentage of patients who developed AF/AFL for the first 7 postoperative days after cardiac surgery. Of those patients the majority presented with de novo AF/AFL within the first 3 postoperative days. The log-rank-test showed no significant difference in the incidence of AF/AFL between the nLP and nHP groups.

Another limitation is the generalizability to the general ward, in which electrolyte levels cannot be as strictly monitored as in the ICU. In addition, few ICUs use a computerized potassium replacement protocol such as GRIP-II. In addition, the ICU stay was relatively short, limiting the differential effect of the treatment arms. However, also in patients admitted to the ICU for a longer period of time, there were no differences in the occurrence of AF/AFL. Because continuous monitoring for AF/AFL was not always performed, the true incidence of AF/AFL may have been higher.

| Subgroup | | Number of patients | | Number of events | | Relative risk |
|---|---|---|---|---|---|---|
| | | nLP | nHP | nLP | nHP | (95%CI) |
| Cardiothoracic surgery *primary endpoint* | | 447 | 463 | 172 (38%) | 188 (41%) | 0.95 (0.80-1.12) |
| Sex | Male | 300 | 311 | 113 (38%) | 128 (41%) | 0.92 (0.75-1.10) |
| | Female | 147 | 152 | 59 (40%) | 60 (40%) | 1.02 (0.77-1.34) |
| Age (years) | <65 | 169 | 185 | 42 (25%) | 59 (32%) | 0.78 (0.56-1.09) |
| | >65 | 278 | 278 | 130 (47%) | 129 (46%) | 1.01 (0.84-1.20) |
| Euroscore | <5.0 | 370 | 391 | 131 (35%) | 149 (38%) | 0.93 (0.77-1.12) |
| | >5.0 | 75 | 72 | 41 (55%) | 39 (54%) | 1.01 (0.75-1.36) |
| New-onset AF/AFL | | 362 | 381 | 111 (31%) | 127 (33%) | 0.92 (0.75-1.14) |
| Prior AF/AFL | | 85 | 82 | 61 (72%) | 61 (74%) | 0.97 (0.80-1.16) |
| On-pump | | 300 | 294 | 135 (54%) | 134 (36%) | 0.99 (0.83-1.18) |
| Off-pump | | 147 | 169 | 37 (25%) | 54 (32%) | 0.79 (0.55-1.12) |

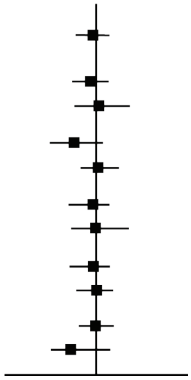

**Figure 5. Subgroup analysis.**

In several subgroups, there were no statistical differences in the incidence of postoperative AF/AFL.

Although it could now be argued that more widely spaced targets should have been compared, our results suggest that even higher potassium administration rates to achieve higher targets have no benefit compared to a low-normal potassium target of 4.0 mmol/L. Despite clearly different computer targets and concomitantly clearly higher potassium administration rates, the levels achieved in the patients tended to be more similar than we expected. This may reflect the inherent stability of the potassium level in many patients and the increased renal loss of potassium in the nHP group. Despite a 73% increase in potassium administration, it resulted in only a 2.6% increase of circulating potassium of 4.22 to 4.33 mmol/L. We believe this indicates that, unlike for example glucose levels, it may not be possible to modify potassium levels at will. Subsequent analysis of patients who were treated for prolonged periods in the ICU suggests that increased potassium administration did not increase the total potassium or the intracellular volume to a detectable degree [21]. In addition, administered potassium is not retained but excreted by the kidneys [22,23]. Finally, there was a higher, although not significant, incidence of severe hyperkalemia in the nHP group. Possibly this is related to the higher number of patients with renal failure in this group. We believe that this also underscores that there may be no benefit of the 4.5 over the 4.0 mmol/L target.

## CONCLUSIONS

In conclusion, 2 different computer-assisted potassium regulation strategies with both targets within the reference range showed no difference in the incidence of AF/AFL after cardiac surgery.

## ACKNOWLEDGEMENTS

Dr Jorik R. Timmer (independent cardiologist, Isala Kliniek, Zwolle, the Netherlands).

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# CHAPTER 4

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# POSTOPERATIVE FLUID RETENTION AFTER HEART SURGERY IS ACCOMPANIED BY A STRONGLY POSITIVE SODIUM BALANCE AND A NEGATIVE POTASSIUM BALANCE

**Physiological Reports 2016;4**

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## ABSTRACT

The conventional model on the distribution of electrolyte infusions states that water will distribute proportionally over both the intracellular (ICV) and extracellular (ECV) volumes, while potassium homes to the ICV and sodium to the ECV. Therefore, total body potassium is the most accurate measure of ICV and thus potassium balances can be used to quantify changes in ICV. In cardiothoracic patients admitted to the ICU we performed complementary balance studies to measure changes in ICV and ECV. In 39 patients, fluid, sodium, potassium and electrolyte-free water (EFW) balances were determined to detect changes in ICV and ECV. Cumulatively over four days, these patients received a mean ±SE infusion of 14.0 ±0.6 L containing 1465 ±79 mmol sodium, 196 ±11 mmol potassium and 2.1 ±0.1 L EFW. This resulted in strongly positive fluid (4.0 ±0.6 L) and sodium (814 ±75 mmol) balances but in negative potassium (-101 ±14 mmol) and EFW (-1.1 ±0.2 L) balances. We subsequently compared potassium balances (528 patients) and fluid balances (117 patients) between patients who were assigned to either a 4.0 or 4.5 mmol/L blood potassium target. Although fluid balances were similar in both groups, the additionally administered potassium (76 ±23 mmol) in the higher target group was fully excreted by the kidneys (70 ±23 mmol). These findings indicate that even in the context of rapid and profound volume expansion neither water nor potassium moves into the ICV.

# INTRODUCTION

In clinical medicine, the conventional model on water and electrolyte distribution states that infused electrolyte-free water (EFW) distributes proportionally over both the intracellular volume (ICV) and the extracellular volume (ECV) [1-3]. The major cations of the ICV and ECV are potassium and sodium, respectively. Critically ill patients receive large electrolyte infusion volumes during treatment in the intensive care unit (ICU). Although retention of sodium and water is well-known to accompany early ICU-treatment [4-7], the effect on potassium balance and ICV has not been studied. Since total body potassium (TBK) is considered as the gold standard for determining ICV [8-12], potassium balances could serve as a quantitative indicator of changes in TBK and thus ICV. We therefore performed fluid, sodium, potassium, and EFW balance studies in ICU patients to quantify changes in ICV and ECV. In addition, we also examined the effect of two different potassium supplementation protocols aiming for either a normal-high or normal-low potassium target on the potassium and fluid balances [12,13].

# METHODS

## STUDY DESIGN

In this study we determined fluid, sodium, potassium, chloride, and EFW balances in critically ill patients admitted after cardiac surgery. The observational retrospective balance studies all involved patients of ≥18 years admitted to a tertiary cardiothoracic ICU from October 2010 until December 2014. Fluid, sodium, potassium, and chloride balances were derived from meticulously recorded input and output, including 24h-urine collections. In all patients, potassium was regulated by our computerized potassium regulation protocol (Glucose and potassium Regulation in Intensive care Patients (GRIP-II)) [9]. Patients were targeted to a serum potassium target of either 4.0 mmol/L (4.0 mmol/L target group) or 4.5 mmol/L (4.5 mmol/L target group) using our GRIP-II protocol. Patients were assigned in alternating blocks during the GRIP-COMPASS (computer-driven glucose and potassium regulation program in intensive care patients with comparison of potassium targets within normokalemic range) trial in substudy C [12]. Directly after completion of this trial our standard target was initially set at 4.5 mmol/L. However, after evaluation of the trial results it was subsequently set at 4.0 mmol/L, since the higher target conferred no clinical benefits [13].

Patients who received renal replacement therapy were excluded from analysis. Our ICU did not have a full electronic patient database management system during the study period. Therefore, all data were derived from reviewing medical and nursing charts. Patients with missing or incomplete charts were excluded. Also, the required 24-h urine analysis was introduced at our ICU during the study period. Thus, we examined the various aspects of balances in complementary substudies A, B and C, which enabled us to gather all information needed in as many patients as possible.

**Table 1. Constants and calculations used in substudy A, B and C**

| | |
|---|---|
| **Substudy A** | |
| *Intake of water, sodium, chloride and potassium* | |
| Intake = infusion fluids + given medication + water (oral) | |
| For electrolytes (mmol): | volume * $[electrolyte]_{administered\ fluid}$ (see Table 2,3) |
| *Output of water, sodium, chloride and potassium* | |
| Output = gastric retention + drain production + insensible perspiration + diuresis (24h urines) | |
| For electolytes (mmol): | volume * $[electrolyte]_{administered\ fluid}$ (see Table 2,3) |
| *Balance of water, sodium, chloride and potassium* | |
| Balance = intake – output | |
| Gastric retention: | volume * $[electrolyte]_{enteral/parenteral\ feeding}$ (see Table 2) |
| Drain fluid loss: | volume * mean blood [electrolyte] |
| Insensible perspiration: | 10 ml/kg/day<br>+ 2.5ml/kg/day per degree centigrade above 37°C<br>(max body weight in equation: 100 kg)<br>* 0.6 if intubated<br>* 0.5 on admission day |
| Temperature: | Mean body temperature of the day (mean of Temperature at 6h and 18h) |
| *Blood (mmol/L)* | |
| Blood potassium reference range: | 3.5- 5.0 |
| Mean blood potassium: | 4.2 |
| Blood sodium reference range: | 135-144 |
| Mean blood chloride: | 108 |
| EFW: | Fluid volume – (($Na^+$ mmol + $K^+$ mmol)/140) |
| This accounts for both the infused and excreted volume. The $Na^+$ and $K^+$ concentrations correspond to the respective volumes. | |
| **Substudy B** | |
| *GRIP potassium intake*= GRIP prescribed potassium chloride in mmol | |
| *Potassium output*= RKE = 24 h potassium excretion in the urine in mmol | |
| *GRIP potassium balance* = GRIP Potassium Intake - Potassium Output | |
| **Substudy C** | |
| *Fluid intake* = infusion fluids + given medication + water (oral) | |
| *Fluid output* = gastric retention + drain production + diuresis (24h urines) | |
| *Balance* = fluid intake – fluid output | |

*Substudy A* evaluated patients in depth to establish the overall extent of cumulative fluid, sodium, potassium, chloride, and EFW retention during the first days after ICU admission. These variables were derived with comprehensive equations including all intake (iv fluids, nutrition, and medication) and excretion or losses (diuresis, insensible perspiration, drained fluids and gastric retention [Table 1-3]). Arterial pH and glucose level were also recorded, since marked changes in these parameters could affect potassium redistribution [15,16]

*Substudy B* evaluated patients who stayed ≥24h at the ICU after cardiac surgery and who were targeted to a serum potassium of either 4.0 or 4.5 mmol/L using our GRIP-II protocol. Patients targeted at 4.0 or 4.5 mmol/L were compared after selection and matching for admission reason, disease severity and length of ICU-stay. The differences between the cumulative GRIP-II prescribed potassium chloride dose and cumulative 24h renal potassium excretion (RKE) were compared between the two target groups (Table 1).

*Substudy C* was a predefined analysis of the GRIP-COMPASS trial [13, 14] in patients with an ICU-stay of >4 days. GRIP-COMPASS assessed the impact of the 4.0 and 4.5 mmol/L potassium targets on the incidence of atrial fibrillation. Here, we analyzed the effect of the 4.0 or the 4.5 mmol/L targets on fluid balances as calculated from intake of iv fluids, nutrition and medication, and losses by diuresis, gastric retention, and drain production (Table 1).

**Table 2. Electrolyte content of infusion fluids used in substudy A**

| | $[K^+]$ (mmol/L) | $[Cl^-]$(mmol/L) | $[Na^+]$ (mmol/L) |
|---|---|---|---|
| **Resuscitation fluids** | | | |
| Voluven® | 0 | 154 | 154 |
| Sterofundin® | 4.02 | 127 | 145 |
| Lactated Ringers | 5.4 | 111 | 134 |
| NaCl 5% | 0 | 856 | 856 |
| Glucose 5% | 0 | 0 | 0 |
| Glucose 50% | 0 | 0 | 0 |
| Glucose 2.5%/NaCl 0.45% | 0 | 77 | 77 |
| NaCl 0.9% | 0 | 154 | 154 |
| **Parenteral/enteral feeding** | | | |
| Nutrison protein plus® | 42.97 | 22.57 | 48.26 |
| Nutrison concentrated® | 49.86 | 22.57 | 43.5 |
| Nutrison multifibre® | 38.36 | 35.27 | 43.5 |
| Nutridrink® | 39.15 | 40.67 | 24.54 |
| Peptisorb® | 38.4 | 35.27 | 43.5 |
| TPN | 30 | 45 | 35 |
| **Blood products** | | | |
| RBC | 40 | 80 | 126 |
| FFP | 2 | 80 | 172 |
| Thrombocyte concentrate | 2 | 70 | 120 |
| Cirrestor blood | 4 | 0 | 140 |
| Cell saver blood | 0 | 100 | 140 |
| Albumin 20% | 0 | 100 | 100 |
| Fibrinogen | 0 | 0 | 71 |
| Thrombocyte concentrate | 2 | 70 | 120 |

## DATA COLLECTION

Analyzed data included basic demographics, reason of admission, acute physiology and chronic health evaluation (APACHE-IV) score for disease severity, acute kidney injury according to the KDIGO AKI criteria [17] and in-hospital mortality. All electrolyte, glucose and pH values, determined in blood or 24-h urine during the first four ICU days were recorded. Samples that displayed hemolysis or otherwise were deemed less reliable, were excluded from analysis.

## BALANCE CALCULATIONS

Fluid and electrolyte balances were derived from patient charts taking the electrolyte content of administered fluids, medication and nutrition into account (Tables 1-3). Insensible perspiration was defined as loss through the skin by evaporation and evaporative water loss from the respiratory tract [18]. We did not take losses via sweat and stool into account.

We corrected for intubation, since loss of fluid will be lower when intubated. Since the admission day is typically not a full day in most cases, this was corrected for in the calculated insensible perspiration.

EFW was determined for both the administered and the lost or excreted volumes by taking the total infused or excreted volume and subtracting the total amount of Na+ and K+ infused or excreted [1,6]. This accounts for both the administered and excreted volume. Na+ and K+ concentrations of 140 mmol/L were used to determine corresponding electrolyte containing volumes. EFW was estimated only on the basis of the cations Na+ and K+. Other cations (e.g. $Ca^{++}$ and $Mg^{++}$) were not taken into consideration since these cations form only a minor fraction of administred fluids. Also, ICV and ECV contain only minor amounts of these cations in a readily exchangeable form.

## STATISTICAL ANALYSIS

Means are given ±SE, unless indicated otherwise, medians with interquartile range (IQR). Baseline characteristics between groups were compared using a chi-square or a Mann-Whitney *U*-test. Balances and electrolyte levels were compared with the Student's *t*-test. A two-sided $P < 0.05$ was considered significant. Balance calculations were performed with a spreadsheet (Excel, Microsoft, Redmond, WA) and statistical analyses were performed with SPSS 22 (IBM, Chicago, IL).

## STUDY APPROVAL

The data analysis in this study was performed in accordance with the guidelines as outlined in Dutch legislation. The study was approved by the medical ethics committee (IRB) of our institution (Medisch Ethische Toetsingcommissie, METc 2015.089). As a retrospective study of routinely collected and anonymized data, informed consent was not required by our IRB. The GRIP-COMPASS trial is registered at Clinicaltrials.gov (NCT01085071).

**Table 3. Solutions used to dissolve frequently used medication in substudy A**

| Type of medication | Dissolved in infusion fluid* |
|---|---|
| Propofol 2% | None |
| Midazolam 100mg/50 ml | NaCl 0.9% |
| Morphine 100mg/50 ml | NaCl 0.9% |
| Insulin 50 IU/50 ml | NaCl 0.9% |
| Noradrenaline 10 mg/50ml | Glucose 5% |
| Adrenaline 10 mg/50 ml | NaCl 0.9% |
| Dobutamine 250mg/50ml | NaCl 0.9% |
| Dopamine 200mg/50 ml | NaCl 0.9% |
| Amiodarone 600mg/50 ml | Glucose 5% |
| Nicardipin 10 mg/50 ml | NaCl 0.9% |
| Milrinone 10 mg/50 ml | NaCl 0.9% |
| Magnesium sulfate | NaCl 0.9% |
| Furosemide 80 mg/50 ml | NaCl 0.9% |
| Nitroglycerin 10 mg/50 ml | NaCl 0.9% |
| Vasopressin 40 U/40 ml | NaCl 0.9% |
| Tacrolimus 2mg/50 ml | NaCl 0.9% |
| Sodium phosphate | NaCl 0.9% |
| Dexmedetomidine | Glucose 5% |
| Clonidine 600 ug/50 ml | NaCl 0.9% |
| Hydrocortisone 200 mg/50 ml | NaCl 0.9% |
| Heparin 20,000 IU/50 ml | NaCl 0.9% |
| Piperacillin/Tazobactam (4/500) | Water ($[Na^+]_{end}$ =196 mmol/L) |
| Fluxocacillin | NaCl 0.9% ($[Na^+]_{end}$ =418 mmol/L) |
| Naloxone | NaCl 0.9% |
| Tranexaminic acid | NaCl 0.9% |
| Labetalol 250 mg/50 ml | None |
| Mycophenolate mofetil | Glucose 5% |
| Ganciclovir | NaCl 0.9% |
| Levosimendan | Glucose 5% |
| Protamine | NaCl 0.9% |
| Phenylephrine | NaCl 0.9% |

*Infusion fluids according to our institutions protocol.

# RESULTS

## SUBSTUDY A: COMPREHENSIVE BALANCE ANALYSIS

Cumulative intake and balances were collected of 39 ICU patients (Table 4) for a four day period. Over this period, large amounts of fluid (14.0 ±0.6 L), EFW (2.0 ±0.1 L), sodium (1,465 ±79 mmol), potassium (196 ±11 mmol), and chloride (1,408 ±69 mmol) were administered (Figure 1A). A positive cumulative fluid balance of +4.0 ±0.6 L was seen with positive sodium and chloride balances of +814 ±75 and +569 ±83 mmol, respectively. In contrast, there was a net potassium balance of -101 ±14 mmol and a net EFW balance of -1.1 ±0.2 L (Figure 1B).

Blood electrolyte concentrations were stable during the study period (Figure 2A). Glucose levels were mildly hyperglycemic with a decrease of 1.5 mmol over the first 4 ICU days (Figure 2B). Arterial pH levels stayed within the reference range (Figure 2B).

## SUBSTUDY B: EFFECT OF TWO DIFFERENT POTASSIUM TARGETS ON POTASSIUM BALANCE

GRIP-prescribed potassium infusion, RKE and potassium balances were determined for 526 cardiothoracic ICU patients (229 patients targeted at the 4.0 mmol/L potassium target and 297 patients targeted at 4.5 mmol/L potassium target) with no baseline differences (Table 4). The cumulative infused potassium dose was 76 ±23 mmol higher (Figure 3A) and the RKE was 70 ±23 mmol higher in the 4.5 mmol/L target group compared to the 4.0 mmol/L target group (Figure 3B).

Both groups showed similar negative potassium balances ($P = 0.42$, Figure 3C). Furthermore, blood potassium levels only showed a slight difference between both groups ($P < 0.001$; Figure 3D).

## SUBSTUDY C: EFFECT OF TWO DIFFERENT POTASSIUM TARGETS ON FLUID BALANCE

Fluid balances in 117 patients (54 patients targeted at the 4.0 mmol/L potassium target and 63 patients targeted at the 4.5 mmol/L potassium target) were examined. The patient groups had similar baseline characteristics (Table 4) and were admitted for at least 5 ICU days with a median of 10 ICU days. Net fluid balances after 4 ICU days did not differ between the two groups (6.3 ±0.4 and 6.3 ±0.4 L respectively; $P = 0.61$) despite receiving significantly different amounts of potassium (Figure 4).

## DISCUSSION

In this first study using comprehensive balances to examine the conventional model on the distribution of fluid and electrolytes over the ECV and ICV, we found a rapid and profound volume expansion of the ECV, while the ICV did not expand.

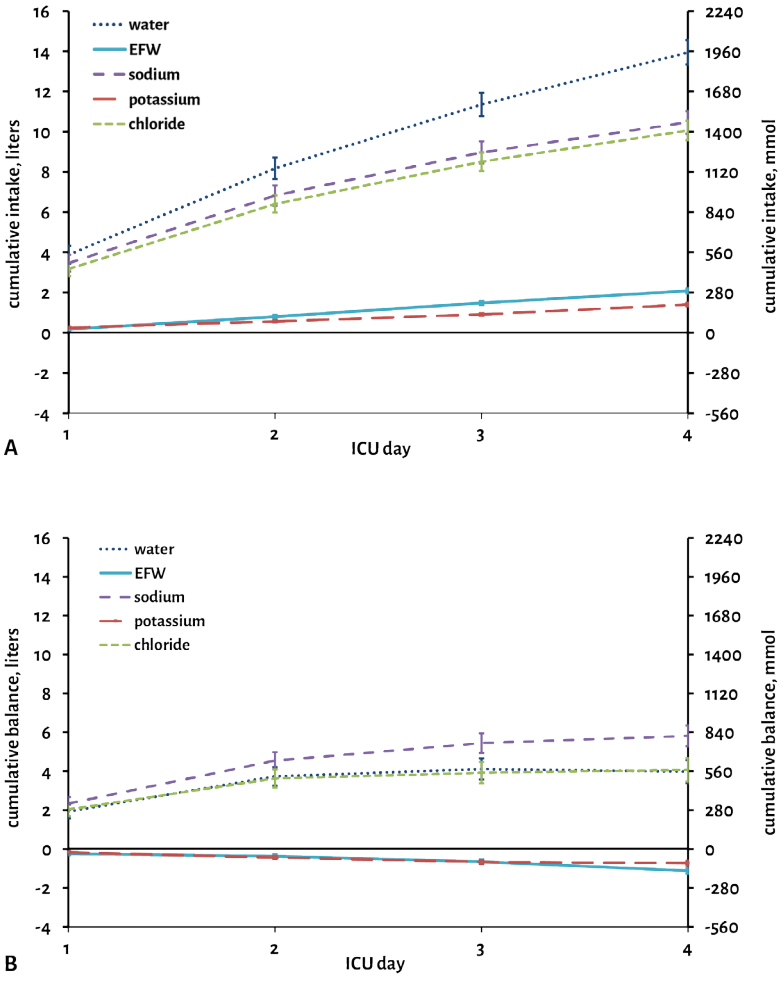


**Figure 1. Cumulative fluid and electrolyte intake and balances in 39 patients in substudy A over the first 4 ICU days.**
All panels depict the mean ±SE for the first 4 ICU days. The 2L and 280 mmol multiples on two Y-axes were chosen to match the normal [Na+] of 140 mmol per 1L, in order to reflect the associated volumes of the intracellular volumes (ICV) and extracellular volumes (ECV).

A. Cumulative intakes show that patients received considerable amounts of fluid, sodium, and chloride as well as potassium and electrolyte-free water (EFW).

B. Cumulative balances show that fluid, sodium, and chloride were retained, but no retention of EFW and potassium occurred. This indicates that ICV remains constant or even shrinks, while the ECV is expanding.

In substudy A, we observed a large cumulative positive balance of fluids, sodium, and chloride, whereas there was a negative balance of both potassium and EFW. This indicates that no increase of the ICV occurred, since such an increase in ICV should have been accompanied by intracellular potassium retention and thus a positive potassium balance. Additionally, blood electrolytes remained stable during this period. Since intra- and extracellular osmolality are essentially equal, this corroborates that no increase in ICV occurred. Both the renal excretion of all the additionally administered potassium in patients targeted at 4.5 mmol/L in substudy B, as well as the absence of more positive fluid balances in patients targeted at 4.5 mmol/L in substudy C underscore that the ICV is not affected by additionally administered potassium. That the extra administered potassium is not retained but excreted, also explains the similarity in potassium levels that was observed in the prospective GRIP-COMPASS trial (4.22 ±0.36 vs. 4.33 ±0.36 mmol/L; $P < 0.001$) [13,14]. In fact, the overall negative potassium balance implies a decrease in TBK and thus a contraction of the ICV. This has been observed in trauma patients [9]. A major contributor to the loss of ICV and thus potassium is the rapid breakdown of striated muscle tissue that is frequently observed in catabolic critically ill patients [9,10,12].

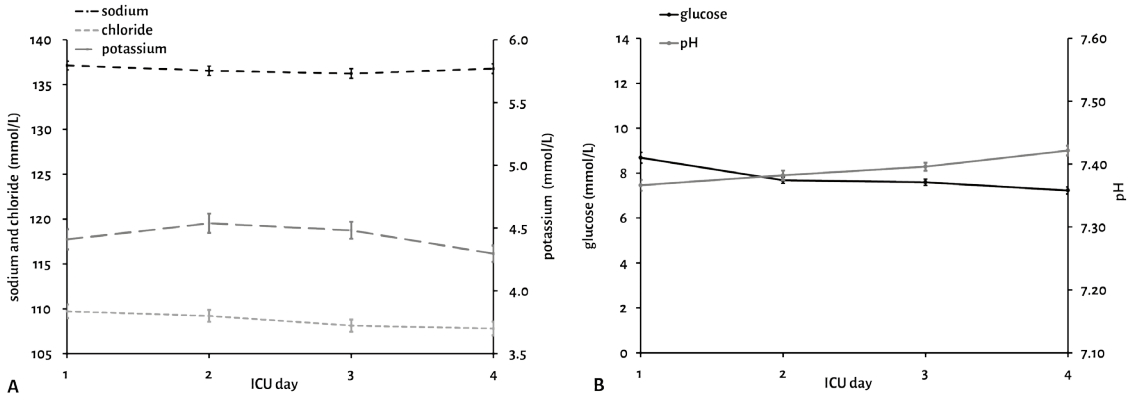


**Figure 2. Circulating electrolyte, glucose, and pH levels in substudy A.**

A. Mean ±SE circulating concentrations of sodium (reference range 135-145 mmol/L), potassium (3.5-5.0 mmol/L) and chloride (97-107 mmol/L) are shown. During the first 4 ICU days, electrolyte concentrations were stable (Kruskal-Wallis test; $P$ = NS).

B. Mean ±SE circulating concentrations of glucose (reference range 4.0-6.4 mmol/L) and pH (7.35-7.45 mol/L) are shown. During the first 4 ICU days, glucose levels decreased, while pH showed a small rise (both glucose and pH; Kruskal-Wallis test; $P < 0.001$).

A perfect quantitative measurement for the ICV does not exist. However, determination of TBK is still considered the best measurement of ICV [8-12]. The current gold standard to assess TBK is scintigraphy of $^{40}K$ exploiting the fact that all naturally occurring potassium contains a minute and constant fraction of $^{40}K$, a radioactive isotope, allowing the determination of TBK with an accuracy in the order of several percent (approximately 100 mmol) [19]. NaBr is sometimes used together with $^{40}K$ to determine the ICV as well as body composition [12, 20], but this method requires a stable body water pool size rendering it unsuitable in ICU patients.

A more popular and less cumbersome, but very indirect and considerably less reliable method to estimate ICV and body composition is bio-impedance analysis (BIA) [11,12]. BIA is difficult to interpret in ICU patients and is particularly poorly suited to detect small changes in ICV. BIA tends to overestimate body cell mass in comparison to TBK by up to 20% and BIA devices have several systematic errors [11]. We are not the first to propose potassium balances as an easy and reliable way to measure changes in TBK [8-10]. But to our knowledge, we are the first to propose potassium balances as a direct measure of changes in ICV in patients who undergo dramatic volume and electrolyte shifts. The measurement of RKE, essential for calculating the potassium balance, is widely available, inexpensive and non-invasive in ICU patients who typically already possess a urinary catheter, which would make this method more feasible for current practice than previously described methods. Thus, whereas $^{40}K$ scintigraphy is most accurate in measuring absolute TBK, the potassium balance method may be optimal to determine changes in TBK and therefore may also serve as an indicator of muscle loss in ICU patients.

An important clinical implication from our observations concerns the strong preference within clinical medicine for sodium-based intravenous fluids over EFW solutions, such as glucose 5%, as the former are considered to expand ECV without significant expansion of ICV as compared to EFW solutions [1-3]. Large infusions of sodium-based fluids frequently lead to sodium accumulation and hypernatremia in patients. Hypernatremia in the ICU is thus largely iatrogenic and it has a strong correlation with negative outcomes [5,6,21,22]. In this study we found no indicators of ICV expansion following administration of EFW. Consequently the need for so-called "physiological" sodium-based infusion fluids (i.e.,130 to 154 mmol/L) can be called into question. However, this does require further investigation since our study was not designed to directly compare different fluid regimens (e.g. sodium-free solutions, low-chloride solutions). If this is also applicable to patients outside of the ICU who receive iv infusions, cannot be concluded yet.

Although major textbooks on physiology [2] and electrolyte and water pathophysiology [1] and a recent review [3] claim that EFW distributes proportionally over the ICV and ECV (Figure 5A-D), this concept has not been verified in critically ill patients who require extensive iv fluid administration in the context of a systemic inflammatory response. This conventional model has its origins in *ex vivo* erythrocyte experiments, first executed by William Hewson in 1773 [23]. Hewson's observations that erythrocytes swell in water and shrink in a hypertonic solution would later lead to recognition of osmotic pressure as a key determinant of cellular volume. Although very important from a mechanistic point-of-view, these in vitro experiments where cells are abruptly exposed to extremely hypo- or hyperosmolar solutions cannot be extrapolated to changes *in vivo*, where cells are more gradually exposed to less extreme osmotic stress.

**Table 4. Patient characteristics of substudies A, B, and C[a]**

| | Substudy A | Substudy B | | | Substudy C | | |
|---|---|---|---|---|---|---|---|
| | | 4.0 | 4.5 | *P* | 4.0 | 4.5 | *P* |
| Age,yr, mean (SD) | 65 (15) | 67 (12) | 67 (13) | 0.52 | 68 (11) | 63 (17) | 0.30 |
| Sex, male | 29 (74%) | 149 (65%) | 210 (71%) | 0.17 | 25 (46%) | 42 (67%) | 0.03 |
| Reason of admission | | | | 0.19 | | | 0.27 |
| *Cardiothoracic surgery* | 32 (82%) | 211 (95%) | 263 (89%) | | 42 (78%) | 54 (86%) | |
| *Trauma* | 1 (3%) | 3 (1%) | 2 (1%) | | 0 (0%) | (0%) | |
| *Vascular surgery* | 1 (3%) | 0 (0%) | 0 (0%) | | 0 (0%) | (0%) | |
| *Miscellaneous* | 5 (13%) | 15 (7%) | 32 (11%) | | 12 (22%) | 9 (14%) | |
| LOS ICU, d | 7.0 (4.0-13.1) | 4.7 (2.8-8.0) | 4.7 (3.0-8.9) | 0.28 | 10.0 (5.7-19.9) | 9.8 (4.9-15.6) | 0.41 |
| APACHE-IV | 61 (45-72)[b] | 58 (47-67) | 59 (45-71)c | 0.56 | 57 (49-69) | 52 (42-65)[e] | 0.07 |
| Hospital mortality | 4 (10%) | 22 (10%) | 28 (9%) | 0.95 | 12 (22%) | 10 (16%) | 0.38 |
| AKI | 11 (28%) | 78 (36%) | 82 (32%)[d] | 0.44 | 12 (26%) | 26 (45%)[e] | 0.04 |
| *Stage 1* | 6 (55%) | 45 (58%) | 49 (60%) | | 6 (50%) | 16 (36%) | |
| *Stage 2* | 3 (27%) | 19 (24%) | 16 (20%) | | 6 (50%) | 9 (20%) | |
| *Stage 3* | 2 (18%) | 14 (18%) | 17 (21%) | | 0 (0%) | 1 (2%) | |
| Diuretic use | 25 (64%) | - | - | | 18 (33%) | 26 (41%) | 0.38 |
| pH, median (IQR) | 7.40 (7.37-7.41) | - | - | | - | - | |
| Glucose, mmol/L | 7.7 (7.4-7.9) | - | - | | - | - | |

[a] *AKI*, acute kidney injury; *APACHE-IV*, acute physiology and chronic health evaluation-IV; *LOS*, length of stay; *ICU*, intensive care unit; *IQR*, interquartile range; [b] for 33 (85%) patients; [c] for 486 (92%) patients; [d] for 471 (90%) patients; [e] for 105 (90%) patients.

Maintaining a constant volume, however, is critical for cellular homeostasis since volume changes affect many critical metabolic and signalling processes [24-26]. Most life forms, from bacteria to eukaryotes, have developed evolutionarily highly conserved mechanisms to rapidly adjust the concentration of so-called osmolytes [24-29]. Osmolytes are comparatively inert intracellular molecules including sugars, polyols, amino acids, urea and methylamines, that can be generated and removed on short notice to avert shrinking and swelling in hyper-osmolar or hypo-osmolar environments. The initial responses on changing extracellular environments are regulatory volume decrease or regulatory volume increase, in which the cell is forced to release or gain potassium, which triggers the generation or clearance of non-essential osmolytes, in order to restore the cell volume [26,29]. Figure 5E-H shows an alternative model that is both compatible with extensive evidence from cell biology on the role of osmolytes and our findings in vivo. The key difference of the alternative model compared to the conventional model is the relative constancy of the ICV.

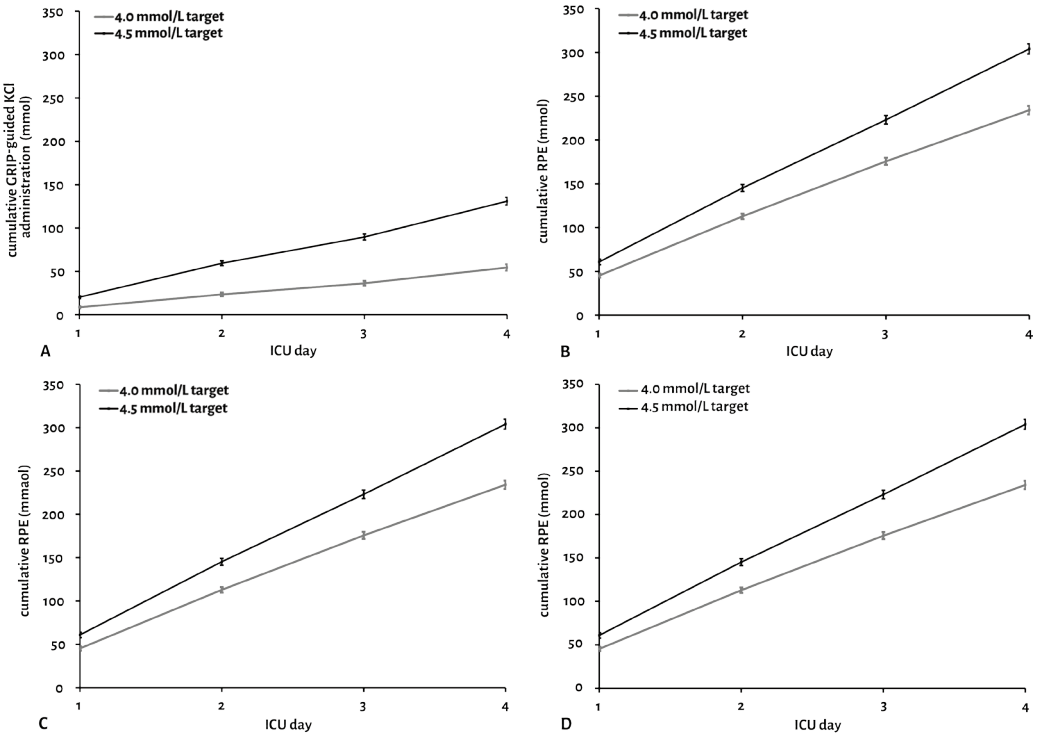


**Figure 3. Potassium infusion, excretion, balances, and blood potassium in substudy B for both the 4.0 (n=920) and 4.5 mmol/L target groups (n=1,162).**

All panels depict the mean ±SE for the first 4 ICU days.

A. Cumulative potassium infusion with the 4.5 mmol/L target group receiving 76 mmol (42%) more potassium than the 4.0 group (Student's *t*-test; $P < 0.001$).

B. Cumulative potassium excretion, with the 4.5 mmol/L target group excreting 70 mmol more (Student's t-test; $P < 0.001$).

C. Cumulative potassium balances are progressively negative. The similarity of the two target groups indicates that the additionally infuse potassium is not retained (Student's *t*-test; $P = 0.42$).

D. Blood potassium was only slightly higher in the 4.5 mmol/L target group despite a 42% higher potassium administration in this group compared to the 4.0 mmol/L target group. The mean blood potassium concentration only differed 0.07 mmol between the two groups (Student's t-test; $P < 0.001$).

The "*milieu interieur*" that animals possess (i.e., the ECV) varies its volume and osmolarity while cells maintain constant volume by adapting the osmolyte concentration. Note that both simplified models shown in Figure 5, do not take structural loss of striated muscle tissue and consequently diminished ICV into account [9,10].

Our study has several limitations. As a retrospective study, many variations in standard care could not be controlled for. Since we did not possess a patient database management system during the study, very time-consuming calculations of balances from non-electronic patient charts had to be performed. The later introduction of routine 24-h urine analysis led us to split our study into three complementary substudies to obtain the relevant data. On the other

hand, ICUs that regularly perform the inexpensive yet accurate 24-h urine analyses and that do possess a patient database management system could automatically determine the relevant balances in nearly real time. Although we meticulously determined the electrolyte and fluid balances in substudy A, we had to make several assumptions such as those regarding insensible water losses. However, given the consistent and marked results, we conclude that errors introduced by these assumptions will only slightly affect the overall differences or the absence of differences in the observed balances. We did not account for fecal and other potassium losses. Inclusion of these unmeasured losses would have resulted in even more profound potassium losses, indicative of an even larger decrease in ICV. Significant changes in glucose and pH are known to alter the distribution of potassium [15, 16]. As described, pH was stable and mostly in the normal range, glucose was only mildly increased.

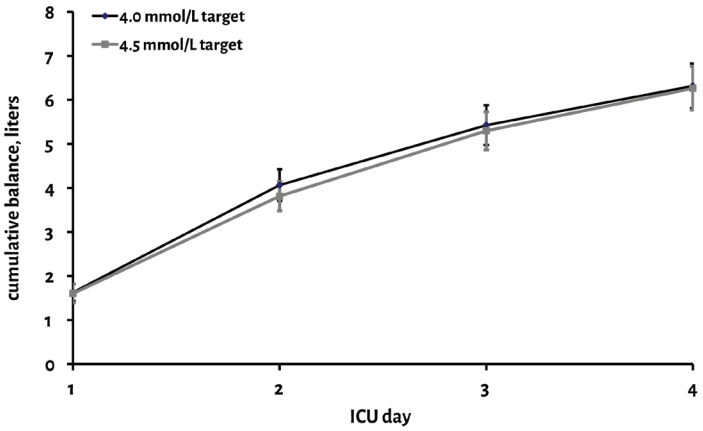


**Figure 4. Cumulative fluid balances in patients in substudy C.**
Mean ±SE cumulative fluid balances (i.e., net fluid received) for the first 4 ICU days for both the 4.0 (n=54) and 4.5 (n=63) mmol/L target group are shown. Despite a higher potassium administration rate in the 4.5-group, the strongly positive fluid balances did not differ between the 4.0 and 4.5 mmol/L target groups (Student's *t*-test; $P = 0.61$).

We therefore believe that these factors are unlikely to have affected potassium distribution. Data on the perioperative phase would have been very interesting, but balance information during surgery was incomplete, thus we could only assess the postoperative phase.

It would be interesting to elucidate the counterregulatory mechanisms that interfered with actually achieving the 4.0 and 4.5 targets, including factors that control RKE in response to higher potassium loads or pharmacological interventions. But this was neither the goal nor feasible in the current study. With respect to this issue, it should be stressed that a key methodological advantage of balance studies is that they do not require any specific assumption on the obviously complex underlying homeostatic systems. Prospective studies in patients who do not have such large fluid requirements and who do not display such pronounced loss of muscle mass as our patients would be welcome. In such patients balance studies could compare the effects of electrolyte-based fluids (e.g. NaCl 0.9%) with more EFW-based fluids (e.g. NaCl 0.45%/glucose 2.5%).

In conclusion, in this first study to comprehensively examine fluid and electrolyte balances in patients during marked volume expansion after ICU admission, we could not demonstrate retention of administered EFW and potassium. Moreover, significant potassium losses were observed, indicating ICV contraction. On the other hand, administered sodium and accompanying fluids were retained, indicating concomitant ECV expansion.

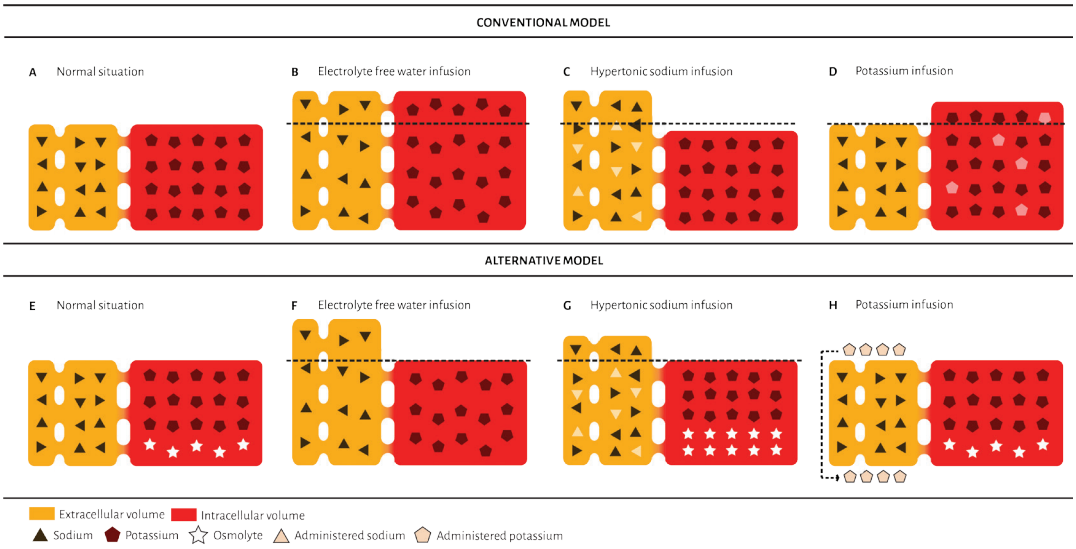


**Figure 5. Conventional and alternative simplified models on water, sodium, and potassium distribution.**

Note that both models do not include muscle loss, causing a "structural decrease" of the ICV. Under either model, water, potassium, and sodium are freely exchanged between the extracellular volume (ECV; yellow; plasma and interstitium) and intracellular volume (ICV; red), governed by physicochemical principles.

A through D. Conventional model depicting the normal distribution of sodium (triangles) and potassium (pentagons).

B. Water distribution after the administration of electrolyte-free water (EFW; e.g. glucose 5% infusion). The additional water is proportionally distributed over the ECV and ICV.

C. Administration of a hypertonic sodium infusion, which homes to the ECV. The osmotic equilibrium is achieved by the redistribution of water from the ICV to the ECV.

D. Administration of an isotonic potassium infusion, that in case the potassium is retained by the body, should home to the ICV. As this is a simplified model, the additional response to the potassium infusion namely the extrusion of sodium is left out.

E through H: alternative model that incorporates intracellular osmolytes (stars), which are osmotically active solutes that are dynamically generated or cleared by the cell. The ICV is kept constant by varying the intracellular osmolyte content to match extracellular osmolarity.

F. Water distribution after administration of EFW. Note that the ICV has cleared its osmolytes to keep its volume constant and maintain iso-osmolarity with the ECV. G. A hypertonic sodium infusion stays in the ECV. The ICV generates osmolytes to keep its volume constant and increase its osmotic pressure to the same levels as the ECV.

H. An isotonic potassium infusion does not enter the ICV and additional potassium is thus renally excreted.

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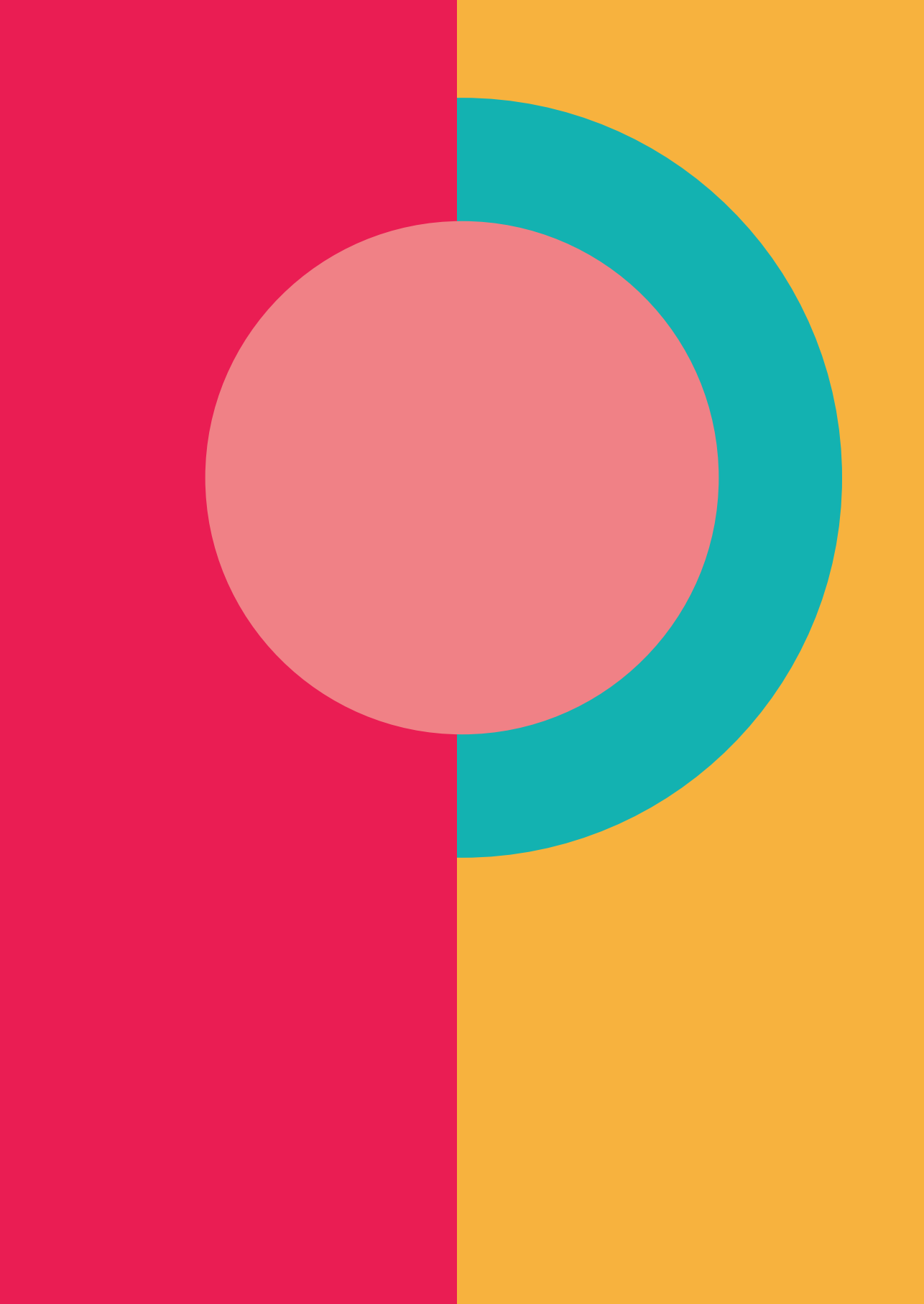

# CHAPTER 5

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# OPPOSITE ACUTE POTASSIUM AND SODIUM SHIFTS DURING TRANSPLANTATION OF HYPOTHERMIC MACHINE PERFUSED DONOR LIVERS

**American Journal of Transplantation 2019;19(4):1061-71**

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**Both authors contributed equally*

## ABSTRACT

Liver transplantation is frequently associated with hyperkalemia, especially after graft reperfusion. Dual hypothermic oxygenated machine perfusion (DHOPE) reduces ischemia/reperfusion injury and improves graft function, compared to conventional static cold storage (SCS). We examined the effect of DHOPE on *ex situ* and *in vivo* shifts of potassium and sodium.

Potassium and sodium shifts were derived from balance measurements in a preclinical study of livers that underwent DHOPE (n=6) or SCS alone (n=9), followed by *ex situ* normothermic reperfusion. Similar measurements were performed in a clinical study of DHOPE-preserved livers (n=10) and control livers that were transplanted after SCS only (n=9).

During DHOPE, preclinical and clinical livers released a mean of 17±2 and 34±6 mmol potassium and took up 25±9 and 24±14 mmol sodium, respectively. After subsequent normothermic reperfusion, DHOPE-preserved livers took up a mean of 19±3 mmol potassium, while controls released 8±5 mmol potassium. During liver transplantation, blood potassium levels decreased upon reperfusion of DHOPE-preserved livers while levels increased after reperfusion of SCS-preserved liver, delta potassium levels were -0.77±0.20 vs. +0.64 ±0.37 mmol/L, respectively ($P = 0.002$).

While hyperkalemia is generally anticipated during transplantation of SCS-preserved livers, reperfusion of hypothermic machine perfused livers can lead to decreased blood potassium or even hypokalemia in the recipient.

# INTRODUCTION

Liver transplantation is frequently accompanied by acute hyperkalemia during reperfusion, which may lead to life-threatening arrhythmia. Several factors are known to contribute to hyperkalemia during liver transplantation, including the release of potassium rich preservation solution, cell lysis during graft reperfusion, metabolic acidosis, and massive transfusion of red blood cells [1-4]. To counteract an anticipated acute rise of potassium after graft reperfusion, anesthesiologists may take preventive measures, such as the administration of glucose/insulin, bicarbonate, calcium or measures as hyperventilation [5,6].

Recently, end-ischemic hypothermic (oxygenated) machine perfusion of donor livers has been introduced into clinical practice as a new method of organ preservation. Compared to SCS alone, additional graft preservation via hypothermic (oxygenated) machine perfusion reduces ischemia/reperfusion injury of liver grafts during transplantation [7-9]. The perfusion fluid that is currently used in Europe and the US for hypothermic machine perfusion is Belzer's University of Wisconsin (UW) machine perfusion solution. Compared to UW *cold storage* solution, UW *machine perfusion* solution contains more sodium (100 mmol/L vs 29 mmol/L) and less potassium (25 mmol/L vs 125 mmol/L), although this is still much higher than the potassium concentration in serum. In our first clinical series of dual hypothermic oxygenated machine perfusion (DHOPE) of donor livers we noted that, in contrast to SCS-preserved livers, *in vivo* graft reperfusion did not result in acute hyperkalemia and in fact was accompanied by hypokalemia in three out of ten recipients [9]. Little is known about cation (potassium and sodium) shifts in the liver during *ex situ* machine perfusion or during reperfusion in the recipient. As *ex situ* machine perfusion involves a closed circuit, this allows a direct calculation of cation uptake (influx) or release (efflux) by the liver.

The aim of the current study is to determine the effect of DHOPE on potassium and sodium shifts in human donor livers during machine perfusion and subsequent warm reperfusion in both a preclinical *ex situ* reperfusion model as well as in patients.

# METHODS

## STUDY DESIGN

This study consisted of two parts: a preclinical study (part A) using human liver grafts that were declined for transplantation and a clinical study (part B) of patients who received a DHOPE-preserved liver graft. In both the preclinical and clinical study, DHOPE-preserved liver grafts were compared with livers that were preserved with SCS alone (controls). The anonymized data analysis in both substudies was performed in accordance with national guidelines and legislation. The preclinical study protocol was approved by the competent authority for organ donation in the Netherlands, the Dutch Transplantation Foundation (NTS) and by the medical ethical committee of our institution (University Medical Center Groningen, record METc protocol 2012.068). Ethical approval for the clinical study was obtained from the same medical ethical committee (record METc protocol 2014.100). In addition, the study protocol of the clinical study was published in an open access trial registry (www.trialregister.nl; trial ID NTR4493).

**Table 1. Comparison of donor and preservation characteristics of livers in the preclinical study (Part A)**

| | DHOPE (n=6) | Control (n=9) | *P* |
|---|---|---|---|
| **Donor characteristics** | | | |
| Age (years) | 64 (57-70) | 62 (52-64) | 0.29 |
| Sex (male) | 3 (50%) | 6 (67%) | 0.62 |
| Type of donor | | | 0.23 |
| DCD | 6 (100%) | 6 (67%) | |
| DBD | 0 | 3 (33%) | |
| Cause of death | | | 0.57 |
| Cardiovascular | 2 (33%) | 1 (11%) | |
| Post anoxic brain injury | 2 (33%) | 4 (44%) | |
| Trauma | 2 (33%) | 4 (44%) | |
| Reason rejected for transplantation | | | 0.35 |
| Age (DCD >60 years) | 5 (82%) | 4 (44%) | |
| Expected steatosis | 1 (17%) | 3 (33%) | |
| High transaminases | 0 | 1 (11%) | |
| Unknown | 0 | 1 (11%) | |
| **Preservation characteristics** | | | |
| Cold ischemia (min)[a] | 489 (452-513) | 509 (409-660) | 0.72 |
| Time from withdrawal of life support to cold flush (min)[b] | 33 (26-53) | 43 (38-79) | 0.13 |
| Time from circulatory arrest to cold flush (min)[c] | 15 (13-23) | 20 (16-23) | 0.49 |

Data are presented as number (percentage) or median (interquartile range).

*DCD*, donation after circulatory death; *DBD*, donation after brain death.

[a] Cold ischemia time was defined as the interval between start aortic cold flush in the donor until the start of NMP or DHOPE.

[b] The time interval between the discontinuation of mechanical ventilation and the start of aortic cold flush in the donor (international donor warm ischemia time).

[c] The time interval between cardiac arrest and the start of aortic cold flush in the donor.

## ORGAN PROCUREMENT

All livers were procured according to a standard protocol by regional organ procurement teams, using a rapid flush out with ice-cold UW cold storage solution (Bridge-to-Life, Ltd. Northbrook, IL) and subsequent SCS in the same fluid during transportation to our center. The potassium concentration of UW cold storage solution is 125 mmol/L, only slightly lower than the intracellular concentration (140 mmol/L) [10]. This minimizes the passive release of intracellular potassium into the extracellular milieu during SCS [11,12]. Likewise, the sodium concentration in UW cold storage solution is 29 mmol/L, only slightly above the intracellular concentration (10 mmol/L) [10], minimizing influx of sodium.

During the back table procedure, livers were prepared for either machine perfusion in the preclinical (Part A) and clinical study (Part B), or for direct transplantation (controls in clinical study).

## DUAL HYPOTHERMIC OXYGENATED MACHINE PERFUSION (DHOPE)

DHOPE was performed with 3 to 4L of UW machine perfusion solution (potassium concentration 25 mmol/L and sodium concentration 100 mmol/L; Bridge-to-Life, Ltd. Northbrook, IL) using the Liver Assist device (Organ Assist, Groningen, The Netherlands) according to the manufacturer's instructions. Before the start of DHOPE, livers were flushed during the back table procedure with 1L of UW machine perfusion solution to flush out UW cold storage solution. The perfusion fluid was oxygenated to obtain a pO2 of approximately 80 kPa. During DHOPE, portal vein perfusion pressure was set at 4 mmHg and mean arterial perfusion pressure at 25 mmHg.

## PART A. PRECLINICAL STUDY

The preclinical study consisted of a total of 15 human donor livers that were declined for transplantation and offered to our center for research after informed consent had been obtained from the relatives of the donor. Livers were selected from a previous study based on the type of preservation fluid used during organ procurement [13]. Only livers preserved in UW cold storage solution were included in the current study. Livers were divided into two groups: 6 livers underwent 2 hours of DHOPE prior to 6 hours of ex situ normothermic machine perfusion (NMP) to assess liver graft viability and function, and 9 livers underwent 6 hours of NMP without prior perfusion with DHOPE.

NMP was performed using the same Liver Assist device, using a solution based on packed red blood cells and plasma, as described previously [13-15]. Prior to NMP, all livers were flushed with 1L cold NaCl 0.9% solution, followed by 500 mL warm NaCl 0.9% solution to flush out UW cold storage (control livers) or UW machine perfusion solution (DHOPE livers). Oxygenation resulted in a pO2 between 50 and 80k kPa. During NMP perfusion pressures were set at 11 mmHg for the portal vein and a mean of 70 mmHg for the hepatic artery.

## PART B. CLINICAL STUDY

The clinical study included 10 patients undergoing liver transplantation, who received a liver that underwent 2 hours of DHOPE prior to implantation. Similar to the preclinical study, DHOPE was applied for 2 hours after conventional SCS. The control group consisted of 9 patients who underwent transplantation without DHOPE treatment of the liver. They were matched for recipient age (±5 years), donor warm ischemia time (±5 minutes), and MELD score (6-22 or ≥23). Livers were selected from a previously published clinical study [9]. Only livers preserved in UW cold storage during the SCS phase were included.

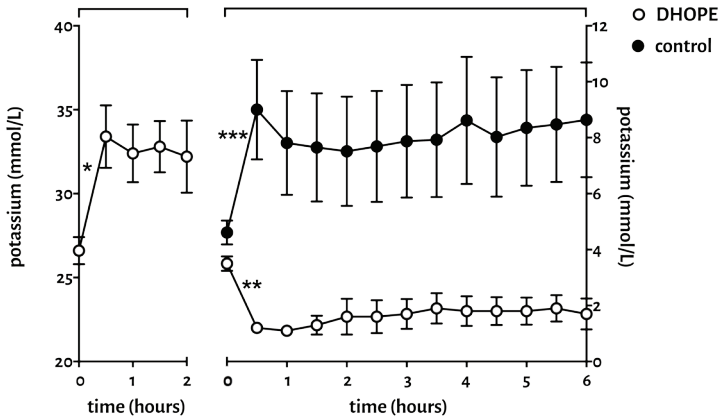


**Figure 1. Mean potassium levels in perfusion fluid during DHOPE and NMP of preclinical livers.**

At baseline (time point zero), samples of the perfusion fluid were taken before the liver was connected to the perfusion device (Liver Assist). Potassium levels increased significantly during the first 30 minutes of DHOPE (*$P$ = 0.03) and stabilized thereafter. During *ex situ* NMP of DHOPE-preserved livers, potassium levels decreased significantly during the first 30 minutes (**$P$ = 0.001) and stabilized thereafter. In contrast during ex situ NMP of control livers, potassium levels increased significantly during the first 30 minutes (***$P$ = 0.04) and stabilized thereafter. Note the different Y-scales for DHOPE and NMP.

All liver grafts were implanted by using the piggy back technique without veno-venous bypass. Graft reperfusion was initiated by restoration of portal venous flow. To avoid hyperkalemia in the recipient, the first 400 mL of blood effluent from the liver was discarded before systemic venous return was established in both DHOPE and control livers. Subsequently the hepatic artery anastomosis was constructed and arterial blood flow to the liver was restored.

## ASSESSMENT OF CATION CONCENTRATIONS AND SHIFTS

During machine perfusion (either DHOPE or NMP), perfusate samples were collected at baseline (prior to connecting liver) and every 30 minutes thereafter. During transplantation, blood samples of the recipient were collected from a non-heparinized arterial line: (a) prior to the anhepatic phase (pre-anhepatic) and (b) during the anhepatic phase, and (c) after portal and (d) arterial reperfusion. Perfusate samples and blood samples were immediately processed for determination of potassium and sodium concentrations, using an ABL 800 point-of-care blood-gas analyzer (Radiometer Medical ApS, Brønshøj, Denmark). Hypokalemia was defined as a potassium concentration <3.5 mmol/L and hyperkalemia as >5.0 mmol/L. All forms of potassium or sodium administration (e.g. potassium chloride or sodium bicarbonate solution) during machine perfusion or during the transplant procedure were recorded.

The hepatic uptake (positive shift or influx) or release (negative shift or efflux) of potassium during *ex situ* machine perfusion was calculated according to the following formula:

$$\text{Potassium shift (mmol)} = ([K^+]_{\text{expected delta}} - [K^+]_{\text{observed delta}}) \cdot V_{\text{perfusion}}$$

where the expected delta in serum potassium concentration was defined as:

$$\text{Expected delta (mmol/L)} = K^+_{\text{administered}} / V_{\text{perfusion}}$$

The observed rise or decrease in potassium concentration was defined as:

$$\text{Observed delta (mmol/L)} = [K^+]_{n+1} - [K^+]_n$$

Here *n* and *n+1* denote two consecutive time points during machine perfusion and V stands for volume of the perfusion fluid. For calculating sodium shifts, similar formulae were used in which $K^+$ was replaced by $Na^+$.

## CORRELATION BETWEEN CHANGES IN CATION LEVELS AND POST REPERFUSION MARKERS OF HEPATIC VIABILITY AND INJURY

In the preclinical study, changes in cation levels upon '*ex situ* reperfusion' (30 minutes after the start of NMP) were correlated with markers of hepatic viability (cellular ATP) and injury (peak perfusate levels of ALT and lactate). In the clinical study, changes of cation levels upon graft reperfusion were correlated with post-operative peak levels of serum ALT and lactate, and prothrombin time (PT) on postoperative day 1.

## CORRELATION BETWEEN CHANGES IN CATION LEVELS AND POST REPERFUSION SYNDROME

One of the more severe hemodynamic disturbances that can occur during liver transplantation is post reperfusion syndrome (PRS). PRS is defined as a drop in mean arterial pressure (MAP) of >30% of baseline values within 5 minutes after graft reperfusion that lasts for at least 1 minute [16]. In the clinical study, changes in cation levels were correlated with changes in MAP and noradrenaline requirement after graft reperfusion.

## STATISTICAL ANALYSIS

Continuous variables are presented as median with interquartile range (IQR), or as mean ±standard error (SE) as appropriate. Categorical variables are presented as number and percentage. Group characteristics were compared between groups using the Mann-Whitney U-test for continuous variables or the chi-square test for categorical variables. Strength and direction of association between two variables were determined by calculating the Spearman's correlation coefficient. Changes in cation levels were compared with a Student *t*-test. A *P* value <0.05 was considered significant. Statistical analyses were performed with SPSS 23.0 (IBM, Chicago, USA).

**Table 2. Correlation between changes in cation levels and post reperfusion markers of hepatic viability and injury in the preclinical study**

| | ΔPotassium (mmol/L) | | ΔSodium (mmol/L) | |
|---|---|---|---|---|
| **Reperfusion levels** | **$r_s$** | ***P*** | **$r_s$** | ***P*** |
| Cellular ATP | -0.85 | <0.001 | 0.58 | 0.048 |
| Peak ALT | 0.81 | <0.001 | -0.61 | 0.02 |
| Peak lactate | 0.92 | <0.001 | -0.72 | 0.008 |

Both DHOPE and control livers were included in a bivariate analysis to correlate changes in potassium and sodium levels upon '*ex situ* reperfusion' (30 minutes after the start of NMP) with levels of cellular energy marker ATP and perfusate peak levels of ALT and lactate. Data are presented as Spearman's correlation coefficient (rs).

ATP, adenosine triphosphate; ALT, alanine aminotransferase; NMP, normothermic machine perfusion.

# RESULTS

## PART A. PRECLINICAL STUDY

### DONOR CHARACTERISTICS

Donor and preservation characteristics are shown in Table 1. There were no significant differences between the two groups in donor characteristics such as donor age, type of donor or donor warm ischemia time (in case of donation after circulatory death [DCD]).

### CATION CONCENTRATIONS AND SHIFTS DURING END-ISCHEMIC DHOPE

During the first 30 minutes of DHOPE, the mean perfusate potassium level increased from 26.6 ±0.8 to 33.4 ±1.9 mmol/L ($P = 0.03$) and levels remained stable thereafter (Figure 1). The total hepatic release of potassium during 2 hours of DHOPE was 17 ±2 mmol.

During the first 30 minutes of DHOPE, mean perfusate sodium level remained stable (102 ±7 to 101 ±6 mmol/L) ($P = 0.91$) but during the remainder of DHOPE levels decreased from 102 ±7 to 94 ±6 mmol/L ($P = 0.06$) (Figure 2). The total hepatic uptake of sodium during 2 hours of DHOPE was 25 ±9 mmol.

### CATION CONCENTRATIONS, SHIFTS AND POTASSIUM-RELATED INTERVENTIONS DURING NMP

During NMP of the DHOPE-preserved livers, potassium levels in the perfusion fluid decreased during the first 30 minutes from 3.5 ±0.3 to 1.2 ±0.1 mmol/L ($P = 0.001$). In livers that underwent NMP without prior DHOPE (controls), potassium levels increased during the first 30 minutes from 4.6 ±0.4 to 9.0 ±1.8 mmol/L ($P = 0.04$). Both groups showed stable perfusate potassium concentrations during the remainder of the NMP (Figure 1).

During NMP of DHOPE-preserved livers, a total hepatic uptake of 19 ±3 mmol of potassium was noted. In control (SCS alone) livers, an opposite potassium shift was observed with a total hepatic release of 8 ±5 mmol. All DHOPE-preserved livers required potassium supplementation during NMP to maintain potassium concentrations within an acceptable range, while in the control livers, only two (13%) needed potassium supplementation ($P < 0.001$).

During NMP of the DHOPE-preserved livers, no changes in sodium perfusate levels were observed in the first 30 minutes of NMP (151 ±1 to 149 ±1 mmol/L, respectively; $P = 0.78$) and levels remained to be stable thereafter. In livers that underwent NMP without prior DHOPE (controls), sodium levels decreased during the first 30 min from 147 ±3 to 139 ±3 mmol/L ($P = 0.02$). Both groups showed stable perfusate sodium concentrations during the remainder of the NMP (Figure 2).

During NMP of DHOPE-preserved livers, a total hepatic release of 7 ±3 mmol of sodium was noted. In control (SCS alone) livers, an opposite sodium shift was noted with a total hepatic uptake of 23 ±9 mmol of sodium.

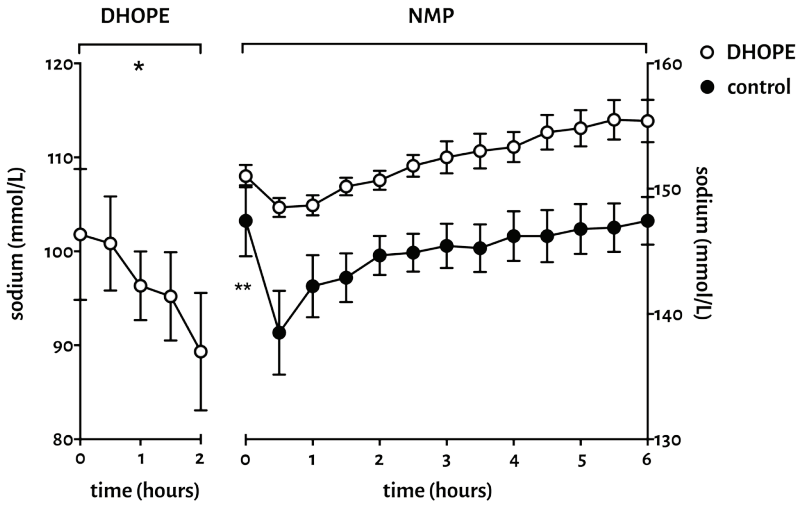


**Figure 2. Mean sodium levels in perfusion fluid during DHOPE and NMP of preclinical livers.**
At baseline (time point zero), samples of the perfusion fluid were taken before the liver as connected to the perfusion device (Liver Assist). Sodium levels remained stable during the first 30 minutes of DHOPE, but levels significantly decreased thereafter (*$P = 0.06$). During ex situ NMP of DHOPE-preserved livers, no changes in sodium perfusate livers, no changes in sodium perfusate levels were observed in the first 30 minutes of NMP and levels remained to be stable thereafter. In contrast, during ex situ NMP of control livers, sodium levels significantly decreased during the first 30 minutes (**$P = 0.02$) and stabilized thereafter. Note the different Y-scales for DHOPE and NMP.

## CORRELATION BETWEEN CHANGES IN CATION LEVELS AND POST REPERFUSION MARKERS OF HEPATIC VIABILITY AND INJURY

After 2 hours of NMP, cellular ATP levels were significantly higher in DHOPE-preserved livers compared to control livers, 88 (50-137) µmol/g vs. 36 (21-57) µmol/g respectively ($P = 0.03$). The change in potassium levels upon ex situ reperfusion correlated negatively with ATP levels after 2 hours of NMP ($P < 0.001$). In other words, an increase in potassium levels upon ex situ reperfusion correlated with low ATP levels (Table 3). In contrast, changes in sodium levels correlated positively with ATP levels after 2 hours of NMP ($P = 0.048$). Moreover, high potassium levels upon ex situ reperfusion strongly predicted high peak ALT levels ($P < 0.001$) and peak lactate levels ($P < 0.001$) (Table 2).

## PART B. CLINICAL STUDY

## PATIENT AND DONOR CHARACTERISTICS

Patient, donor and surgical characteristics are shown in Table 3. There were no significant differences in baseline characteristics or surgical variables between the groups. Most importantly, preoperative serum potassium and sodium concentrations, as well as intra-operative blood loss and transfusion of packed red blood cells did not differ between the two groups.

## CATION CONCENTRATIONS AND SHIFTS DURING END-ISCHEMIC DHOPE

During the first 30 minutes of DHOPE, the potassium perfusate level increased from 25.2 ±0.6 to 33.8 ±2.3 mmol/L ($P = 0.003$), and levels remained stable thereafter (Figure 3). The total hepatic potassium release during 2 hours of DHOPE was 34 ±6 mmol.

During the first 30 minutes of DHOPE, sodium levels slightly decreased from 107 ±3 to 103 ±2, yet this decrease did not reached significance ($P = 0.22$), and sodium levels remained stable thereafter (Figure 4). However, despite absence of a significant drop in sodium levels, the total (calculated) hepatic sodium uptake during 2 hours of DHOPE was still 24 ±14 mmol.

## CATION CONCENTRATIONS DURING IN VIVO REPERFUSION AND POTASSIUM-RELATED INTERVENTIONS

After *in vivo* graft reperfusion, blood potassium levels decreased from 4.7 ±0.2 to 3.9 ±0.3 mmol/L ($P = 0.003$) in recipients of a DHOPE-preserved liver. In recipients of a control (SCS alone) liver, blood potassium levels increased from 4.4 ±0.1 to 5.0 ±0.4 mmol/L ($P = 0.15$; Figure 3). During OLT, three (30%) recipients of a DHOPE-preserved liver required potassium supplementation, while no such supplementation was given to recipients of a control liver ($P = 0.12$).

After *in vivo* graft reperfusion, blood sodium levels slightly increased in recipients of a DHOPE-treated liver (135 ±1 to 137 ±1 mmol/L, $P = 0.04$), whereas levels slightly decreased in control (SCS alone) recipients from 138 ±2 to 137 ±2 mmol/L, yet this did not reach significance ($P = 0.23$; Figure 4).

## CORRELATION BETWEEN CHANGES IN CATION LEVELS AND POST REPERFUSION MARKERS OF HEPATIC VIABILITY AND INJURY

Increased potassium levels (mmol/L) upon portal reperfusion significantly correlated with higher peak serum ALT levels after transplantation ($P = 0.001$). There was no significant correlation between post reperfusion serum potassium levels and lactate levels and post-operative prothrombin times (Table 4).

## CORRELATION BETWEEN CHANGES IN CATION LEVELS AND POST REPERFUSION SYNDROME

*In vivo* reperfusion of DHOPE-preserved livers or control livers, resulted in minimal changes in median MAP (Figure 5). Post reperfusion syndrome occurred in 0 out of 10 patients in the DHOPE group and in 1 out of 7 in the control group ($P = 0.44$). Changes in MAP upon reperfusion did not correlate with changes in potassium and sodium levels (Table 4). Unfortunately, recordings of the MAP and noradrenaline dose around the time of reperfusion were missing in 2 (out of 9) patients in the control group.

During *in vivo* reperfusion of DHOPE-preserved livers, median noradrenaline requirement increased from 0.16 (0.14-0.29) µg/kg/min to 0.24 (0.23-0.48) µg/kg/min ($P = 0.02$). In controls, median noradrenaline requirement increased from 0.14 (0.14-0.29) (µg/kg/min) to 0.27 (0.23-0.38) (µg/kg/min) upon reperfusion, although did this not reach significance ($P = 0.08$) (Figure 5). Interestingly, increased potassium levels and decreased sodium levels upon reperfusion significantly correlated with increased noradrenaline requirement (Table 4).

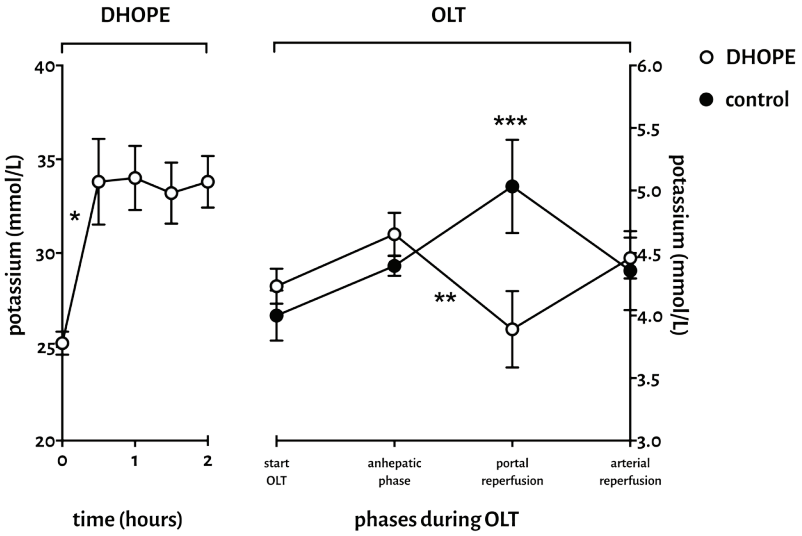


**Figure 3. Mean potassium levels in perfusion fluid during DHOPE and in recipient blood samples during subsequent orthotopic liver transplantation (OLT).**

At baseline (time point zero), samples of the perfusion fluid were taken before the liver was connected to the perfusion device (Liver Assist). Potassium levels in the perfusion fluid increased significantly during the first 30 minutes of DHOPE (*$P < 0.001$), and stabilized thereafter. During OLT of DHOPE-preserved livers, blood potassium levels decreased significantly after reperfusion (**$P = 0.003$). Moreover, at the time of graft reperfusion, blood potassium levels were significantly lower in DHOPE patients when compared to potassium levels at that time point in control patients (***$P = 0.03$). Note the different Y-scales for DHOPE and NMP.

## DISCUSSION

In contrast to transplantation of conventional, SCS-preserved livers, which is accompanied by a risk of acute hyperkalemia, transplantation of livers that underwent hypothermic oxygenated machine perfusion was associated with a decrease in recipient blood potassium levels after graft reperfusion. These findings have clinical consequences for the perioperative management of liver transplant recipients as anesthesiologists and surgeons should anticipate a possible need for potassium administration to maintain normokalemia upon graft reperfusion of a liver graft that underwent hypothermic oxygenated machine perfusion.

To our knowledge, this is the first study in which potassium and sodium shifts after reperfusion of DHOPE-preserved livers were examined. We observed hepatic potassium release during DHOPE and hepatic potassium uptake after warm reperfusion of DHOPE-preserved livers. Hepatic uptake of potassium upon warm reperfusion occurred both ex situ during NMP and *in vivo* during transplantation. In contrast, control livers that underwent only conventional SCS showed potassium release during warm reperfusion. Hepatic cation shifts during DHOPE and subsequent warm reperfusion or during SCS and warm reperfusion are summarized in Figure 6.

Physiologically, the liver serves as a buffer for enteral potassium loads. Cellular potassium uptake requires active transport by the ATP-dependent $Na^+/K^+$-ATPase [4,17]. Low temperatures (8-12 degrees Celsius) during DHOPE are likely to impair optimal function of $Na^+/K^+$-ATPase, thereby facilitating passive potassium release [18]. The total mean hepatic release of potassium during DHOPE varied from 17 mmol in preclinical livers to 34 mmol clinical livers (Figure 5). Also, as a consequence of impaired $Na^+/K^+$-ATPase during DHOPE, the total mean hepatic sodium uptake was 25 to 29 mmol in preclinical and clinical livers, respectively. Moreover, in line with previously published data, cellular ATP levels were significantly higher in DHOPE preserved livers compared to controls upon *ex situ* reperfusion [13]. Furthermore, this study showed that high ATP levels upon reperfusion significantly correlated with decreased potassium. This underlines the potential role of the ATP dependent hepatic potassium uptake in DHOPE-preserved livers. Moreover, in both our preclinical and clinical study, increased potassium levels correlated with high peak ALT levels upon reperfusion. In other words, a decrease in potassium levels upon reperfusion might therefore be an interesting "early prediction" marker of good liver function. However, futures studies are necessary to confirm this.

A decrease in blood potassium levels, as observed after reperfusion of DHOPE-preserved liver grafts, is a remarkable and otherwise rarely observed phenomenon in patients undergoing liver transplantation. One previous study reported a slight decrease in potassium levels after reperfusion of UW-preserved liver grafts compared to histidine-tryptophan-ketoglutarate solution in adult living donor liver transplantations [19]. It must be noted that, due to logistical differences between post-mortal and living donor liver transplantations, cold ischemia times (mean 66 minutes) in this study were substantially shorter than cold ischemia times in our study groups. In pediatric liver transplantation, hypokalemia after graft reperfusion is more commonly seen. The underlying mechanism has yet to be elucidated [20]. Both living donor and pediatric liver transplant procedures can, however, not be compared with our patient group.

The first clinical series of oxygenated hypothermic machine perfusion did not report potassium or sodium concentrations [21]. However, Guarrera, *et al.* published the first clinical series of transplantation of non-oxygenated hypothermic machine perfused (HMP) liver grafts [7]. These authors used a perfusion solution with the same potassium content as Belzer-UW machine perfusion solution (25 mmol/L). Changes in potassium levels during the first 30 minutes of HMP were not reported, but potassium levels were stable at approximately 30 mmol/L during the remainder of HMP. This level of potassium is comparable to the potassium levels in the perfusion fluid during DHOPE in our preclinical and clinical studies. Altogether, this suggests that similar shifts in potassium have occurred in the liver machine perfusions described by Guarrera, et al, although the authors have not specifically noted this in their publication [7].

While DHOPE and NMP constitute closed systems that are well suited to measure cation shifts, this was not possible during reperfusion *in vivo*. Nevertheless, the preclinical and clinical studies collectively point into the same direction and provide an explanation for the observed decrease in blood potassium levels in recipients of a DHOPE-preserved liver.

**Table 3. Comparison of donor and recipient characteristics of transplanted livers (Part B)**

| | DHOPE (n=10) | Control (n=9) | *P* |
|---|---|---|---|
| **Donor characteristics** | | | |
| Age (years) | 53 (45-57) | 55 (50-57) | 0.90 |
| Sex (male) | 5 (50%) | 5 (57%) | 0.46 |
| Type of donor | | | 1.00 |
| DCD | 10 (100%) | 9 (100%) | |
| DBD | 0 | 0 | |
| Cause of death | | | 0.73 |
| Cardiovascular | 3 (30%) | 5 (56%) | |
| Post anoxic brain injury | 3 (30%) | 2 (22%) | |
| Trauma | 4 (40%) | 2 (22%) | |
| **Recipient characteristics** | | | |
| Age (years) | 57 (54-62) | 57 (53-62) | 0.12 |
| Sex (male) | 6 (60%) | 4 (44%) | 1.00 |
| MELD score | 16 (15-22) | 22 (17-25) | 0.12 |
| **Preservation characteristics** | | | |
| Cold ischemia (min)[a] | 311 (282-357) | 430 (424-487) | <0.001 |
| Time from withdrawal of life support to cold flush (min)[b] | 27 (23-43) | 36 (29-55) | 0.46 |
| Time from circulatory arrest to cold flush (min)[c] | 15 (13-17) | 17 (15-19) | 0.41 |
| **Surgical variables** | | | |
| Estimated blood loss (mL) | 3,600 (1,763-4,875) | 2,700 (2,200-6,600) | 0.91 |
| Preoperative serum [$K^+$] (mmol/L) | 4.3 (4.1-4.7) | 3.9 (3.9-4.7) | 0.78 |
| Preoperative serum [$Na^+$] (mmol/L) | 137 (133-141) | 137 (134-141) | 0.28 |
| RBC transfusion (unit) | 3.0 (1.5-7.5) | 3.0 (0.5-8.5) | 0.86 |

Data are presented as median (interquartile range) or numbers (percentages).

*DCD*, donation after circulatory death; *DBD*, donation after brain death; *MELD* score, Model for End-Stage Liver Disease score; *RBC*, Red Blood Cell.

[a] Cold ischemia time was defined as the interval between start of aortic cold flush until start of DHOPE or in-vivo graft reperfusion.

[b] The time interval between the discontinuation of mechanical ventilation and the start of aortic cold flush in the donor (international donor warm ischemia time).

[c] The time interval between cardiac arrest and the start of aortic cold flush in the donor.

As hypothermic oxygenated machine perfusion, e.g, DHOPE and HOPE, are entering the clinical arena as a method to reduce ischemia-reperfusion injury in liver transplantation, it is of utmost importance that transplant anesthesiologists anticipate a decrease rather than an increase in blood potassium concentration after graft reperfusion. Current pre-emptive anti-hyperkalemic measures, such as the use of glucose/insulin and sodium bicarbonate, might aggravate the decrease in blood potassium concentrations after reperfusion of DHOPE-preserved livers. In our study, potassium supplementation was required more frequently during transplantation of a DHOPE-preserved liver, compared to transplantation of a conventional SCS preserved liver. Modified perioperative management is thus appropriate during transplantation of a liver that underwent hypothermic oxygenated machine perfusion.

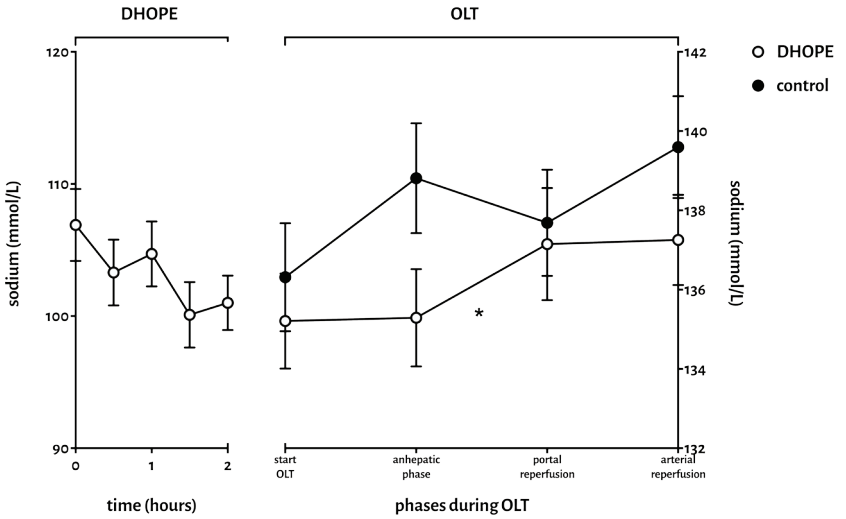


**Figure 4. Mean sodium levels in perfusion fluid during DHOPE and in recipient blood samples during subsequent orthotopic liver transplantation (OLT).**

At baseline (time point zero), samples of the perfusion fluid were taken before the liver was connected to the perfusion device (Liver Assist). Sodium levels in the perfusion fluid slightly decreased, during the first 30 minutes of DHOPE as well as during the remainder of DHOPE, yet not significantly. During OLT of DHOPE-preserved livers, blood sodium levels increased significantly after reperfusion (*$P$ = .04). During OLT of control livers, blood sodium levels slightly decreased after reperfusion, yet not significantly. Note the different Y-scales for DHOPE and NMP.

**Table 4. Correlation between changes in cation levels and post reperfusion syndrome**

| | ΔPotassium (mmol/L) | | ΔSodium (mmol/L) | |
|---|---|---|---|---|
| **Reperfusion levels** | **$r_s$** | ***P*** | **$r_s$** | ***P*** |
| Peak ALT | 0.74 | 0.001 | -0.38 | 0.11 |
| Peak lactate | 0.29 | 0.27 | -0.27 | 0.26 |
| PT (POD 1) | 0.34 | 0.18 | -0.24 | 0.33 |
| ΔMAP | -0.23 | 0.40 | 0.25 | 0.33 |
| ΔNoradrenaline dose | 0.62 | 0.01 | -0.62 | 0.008 |

Both DHOPE and control livers were included in a bivariate analysis to correlate changes potassium and sodium levels upon graft reperfusion with peak levels of ALT and lactate ), and the PT value on postoperative day 1. Changes in cation levels were also correlated with changes in mean arterial pressure (ΔMAP) and changes in noradrenaline dose (Δnoradrenaline dose) upon reperfusion. Data are presented as Spearman's correlation coefficient (rs).

*ALT*, alanine aminotransferase; *MAP*, mean arterial pressure; *PT*, prothrombin time.

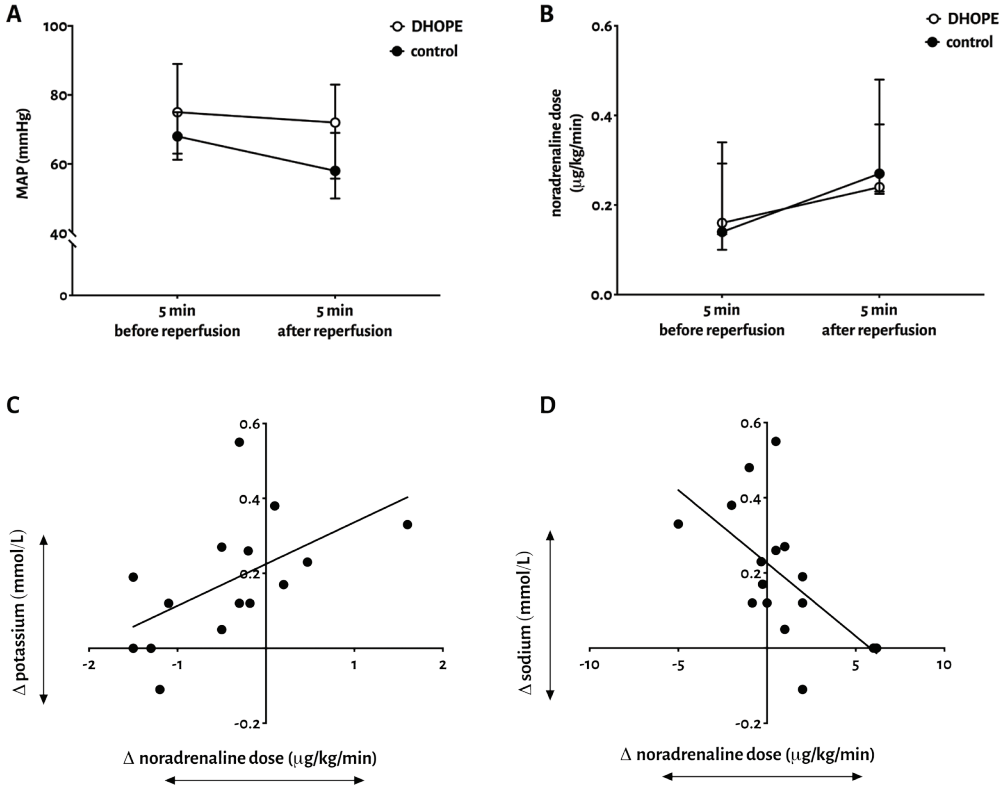


**Figure 5. Changes in intraoperative hemodynamics upon reperfusion.**

No significant changes in mean arterial pressure (MAP) were noted after reperfusion of both DHOPE and control livers (A) while noradrenaline requirements increased in both groups (B). Increased noradrenaline dose upon reperfusion significantly correlated with increased potassium levels (C) and decreased sodium levels (Panel D); $P = .01$ and $P = 0.008$, respectively.

Another clinical challenge that anesthesiologists may encounter during graft reperfusion is hemodynamic instability. While the exact pathophysiology of this post reperfusion syndrome (PRS) is not clearly understood, it has been correlated with high potassium levels and increased ischemia-reperfusion injury [22]. In this study we did not observe PRS in the DHOPE group. In the control group, 1 out of 7 (14%) patients demonstrated PRS, which is in the lower range of the reported incidence of PRS during OLT (varying between 12% and 77%) [23]. In our study, median MAPs remained stable in both groups with adequate increases of the noradrenaline dose. We did, however, observe that increase noradrenaline requirements upon reperfusion correlated with increased potassium levels and decreased sodium levels. It has to be noted that data on MAP and inotropic doses were not complete in 2 out of 9 control patients.

The decrease instead of increase in blood potassium concentration after reperfusion of a DHOPE-preserved liver graft may actually be helpful in patients with concomitant renal insufficiency. Many patients with end-stage liver disease also have some degree of renal failure, making them more prone for difficult to control hyperkalemia. The increase in blood potassium

concentrations after reperfusion of a SCS-preserved liver graft may cause cardiovascular instability due to arrhythmias in these patients and this problem should be less frequent after reperfusion of a DHOPE-preserved liver.

In conclusion, while hyperkalemia is generally anticipated during transplantation of a SCS-preserved liver, reperfusion of a DHOPE-preserved liver is associated with potassium uptake by the liver, which can lead to a decrease in blood potassium concentrations or even hypokalemia. Anesthesiologists and surgical teams should be prepared for this opposite shift in potassium during transplantation.

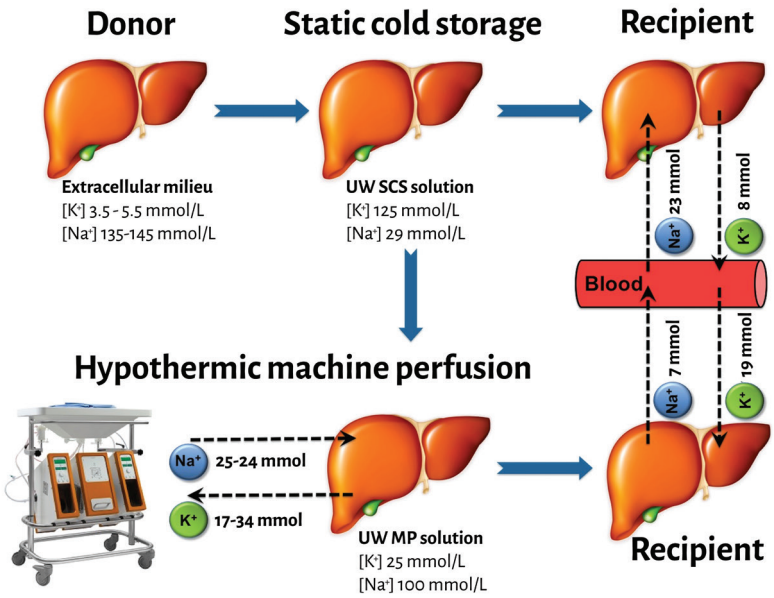


**Figure 6. Overview of potassium and sodium shifts during organ preservation and subsequent warm reperfusion.** This cartoon summarizes cation shifts during hypothermic machine perfusion in both preclinical and clinical livers, and during subsequent warm reperfusion in the preclinical study. During static cold storage (SCS), donor livers were preserved in a high potassium and low sodium preservation solution, containing 125 mmol/L potassium and 29 mmol/L sodium. During warm reperfusion of SCS-preserved livers, a mean total hepatic potassium release of 8 mmol and a mean total hepatic sodium uptake of 23 mmol was observed. During hypothermic oxygenated machine perfusion, a mean total hepatic potassium release of 17 mmol in the preclinical and 34 mmol in the clinical study was noted. Simultaneously, a total hepatic sodium uptake of 25 mmol was noted during hypothermic machine perfusion in the preclinical study and of 24 mmol in the clinical study. Opposite cation shifts were observed during subsequent warm reperfusion of liver grafts. During reperfusion of DHOPE-preserved livers, a total hepatic potassium uptake of 19 mmol and a total hepatic sodium release of 7 mmol was noted, whereas reperfusion of a SCS-preserved livers was associated with a total hepatic release of 8 mmol potassium and a total hepatic uptake of 23 mmol of sodium. These differences in cation shifts explains the risk of a post reperfusion systemic hyperkalemia in recipients of a conventional SCS-preserved liver and a decrease in blood potassium levels in recipients of a DHOPE-preserved liver.
*UW*, University of Wisconsin; *SCS solution*, static cold storage solution; *MP solution*, machine perfusion solution.

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# CHAPTER 6

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# HYPOTHESIS: ANGIOTENSIN AND ALDOSTERONE INHIBITORS HELP IMPROVE OUTCOME IN CHRONIC HEART FAILURE BECAUSE POTASSIUM SPARING PRESERVES SKELETAL MUSCLE MASS

**Submitted**

Lara Hessels, Miriam Zeillemaker-Hoekstra, Maarten W. Nijsten

## ABSTRACT

Cachexia complicates many chronic diseases. In chronic or congestive heart failure (CHF), cachexia independently contributes to decreased survival. Although diuretics have long been part of standard treatment of CHF, the addition of angiotensin and aldosterone antagonists to the standard treatment regimen have considerably improved the outcome of CHF. Both loop diuretics and the upregulation of the renin-angiotensin-aldosterone system caused by CHF induce loss of total body potassium (TBK). In addition to the causal association of loss of muscle mass with loss of TBK, we propose that the reverse mechanism also exists. The known beneficial effects of angiotensin and aldosterone inhibition may partly result from preserved TBK with consequent muscle mass preservation. We propose that monitoring of muscle mass, potassium balances and TBK should be included in future CHF studies to verify this hypothesis and allow further optimization of therapy.

## INTRODUCTION

Cachexia is a serious complication of many chronic diseases, such as cancer, liver cirrhosis and heart failure [1,2]. The loss of skeletal muscle in patients with chronic or congestive heart failure (CHF) is related to impaired survival, independent of other factors [1]. As CHF is currently the third most common chronic comorbidity, cachexia constitutes a public health issue [3]. Prevention of the loss of muscle mass in CHF might improve outcome. We propose a new hypothesis considering an important role of the loss of potassium in cardiac cachexia through both the activation of the renin-angiotensin-aldosterone system (RAAS) and the use of loop diuretics and the potential protective effect of angiotensin and aldosterone inhibition on skeletal muscle mass.

## CHRONIC HEART FAILURE

CHF remains one of the most common, disabling and deadly chronic diseases, with a quality of life lower than many other chronic diseases [4]. The pathophysiology of CHF is complex and multifactorial, with interaction of immune, metabolic and neurohormonal factors which eventually facilitate a chronic catabolic state [3]. The impaired cardiac function in CHF leads to neurohormonal activation through the sympathetic nervous system, RAAS and the natriuretic peptide system [3,5]. The upregulation of both epinephrine and norepinephrine causes a catabolic shift, leading to a higher resting energy expenditure in CHF patients. However, upregulation of the RAAS in CHF has long been seen as the inducer of cachexia, as both angiotensin II and aldosterone are associated with muscle wasting [6] (Figure 1). Currently, it is thought that angiotensin II causes muscle wasting through multiple mechanisms, such as increased oxidative stress, increased protein breakdown, reduced appetite, impaired energy balance and inhibition of satellite cell function and muscle regeneration [3]. Aldosterone is associated with both cardiac and skeletal muscle loss and myocyte apoptosis [6]. It also promotes the retention of sodium, loss of potassium and magnesium, sympathetic activation, parasympathetic inhibition and vascular and myocardial fibrosis [5].

The management of CHF has greatly improved over the last decades. Established components of CHF treatment are loop diuretics, ACE inhibitors, angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA). Loop diuretics are used to prevent fluid and sodium overload in CHF patients. Both ACE inhibitors and ARBs reduce angiotensin II and therefore lead to improvement in symptoms and prolonged survival in CHF patients [6]. In patients with symptomatic heart failure, addition of the MRA spironolactone, leads to an additional reduction of both morbidity and mortality [7].

## TOTAL BODY POTASSIUM

From an evolutionary point of view, humans have never been confronted with potassium scarce diets. Therefore, in contrast to sodium, very limited mechanisms exist to preserve potassium. Potassium is the major cation of the intracellular compartment. A large part of the total body potassium (TBK) resides in skeletal muscle, and radionuclear TBK quantification can be used to measure muscle mass [8]. Cachexia thus logically leads to a reduction in TBK [9,10], which has been observed in other cachectic patient groups. During critical illness, a reduction in both the intracellular volume and TBK is seen [11,12].

Heart failure itself is associated with a loss of TBK [13] (Figure 1). This is not only because of the loss of muscle mass, but also because of intracellular potassium depletion [14], underscoring the constant stress that the intracellular compartment is exposed to in this situation. The potassium depletion in CHF is partly explained by upregulation of the RAAS and therefore increased aldosterone secretion. This loss is then exacerbated by the treatment of CHF with loop diuretics [9]. Several studies have shown that long-term diuretic treatment leads to a decrease in intracellular potassium concentration in skeletal muscle cells [15,16].

An important part of resting energy expenditure is devoted to the maintenance of $Na^+/K^+$ gradients [17]. The constant extra work to maintain these gradients, resulting from mild hypokalemia caused by CHF itself and diuretics, will place additional energetic demands on the already often poorly perfused skeletal muscle and other tissues. Since it is essential that the intracellular potassium concentration is be held above a minimal concentration, a cell only has one strategy left when faced with ongoing potassium loss to the extracellular space, namely to reduce its volume or to go into apoptosis.

A key part of the CHF treatment is targeted against the upregulation of the RAAS and thus may be beneficial in the prevention of TBK decreases and muscle mass (Figure 1). Use of ACE-inhibitors have been associated with a reduction in weight loss in cachectic CHF patients and delayed the development of cachexia by 8 months [1,18]. ARBs might also have a favorable effect on the cachectic effects of RAAS, as found in different mouse models of myopathy that demonstrated an increased muscle strength and muscle regenerative ability after ARB treatment [18].

Several studies show that in both CHF and liver cirrhosis patients, spironolactone added to conventional treatment results in a rise in intracellular potassium, even when this was first depleted [2,19]. Intracellular potassium levels even increased to a concentration similar to those of healthy controls [2]. Also, it has been shown that spironolactone increases exercise tolerance in CHF patients, also suggesting that this increase in intracellular potassium might also impact the quality of muscle [20]. An increase in serum creatinine is often observed after addition of a MRA and this only underscores the beneficial effect of angiotensin and aldosterone inhibition on skeletal muscle [19].

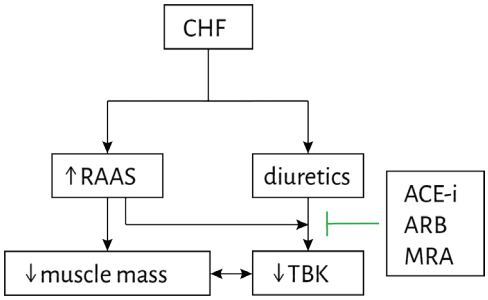


**Figure 1. Schematic depiction of the proposed hypothesis.**

Figure 1 shows a simplified depiction of the proposed hypothesis. CHF induces an upregulation of the RAAS, hereby increasing the loss of TBK. Diuretics, part of standard treatment of CHF, further aggravate this loss. The loss of TBK leads to loss of muscle mass and vice versa. We propose that part of the beneficial effect of angiotensin and aldosterone inhibition results from a preservation of TBK and consequently muscle mass.

## HYPOTHESIS: PRESERVATION OF TBK AND PREVENTION OF CACHEXIA

CHF is accompanied by (intracellular) potassium depletion. Interestingly, nobody has linked this potassium depletion and the success of the angiotensin and aldosterone inhibitors in the treatment of CHF. The beneficial effect of MRAs and the already aldosterone blocking ACE-inhibitors or ARBs may very well be dual: in addition to further counteracting aldosterone secretion, this cocktail may also be muscle sparing (Figure 1). We postulate that the persistent loss of intracellular potassium leads to loss of muscle mass in CHF patients and vice versa.

## TESTING THE HYPOTHESIS

Although several studies have shown that the potassium concentration rises in skeletal muscle after starting MRAs, no study has yet directly demonstrated the relation between intracellular potassium loss and muscle wasting.

It is difficult to assess TBK. The golden standard for TBK is $^{40}K$ scintigraphy, which is a cumbersome and expensive method. However, the absolute value of TBK is not necessarily needed to determine alterations in TBK. Potassium balances might be a much easier and reliable way to assess changes in TBK [10,12]. Monitoring the amount of muscle loss and potassium balances in CHF patients would provide us with more information regarding the association between potassium loss and muscle wasting. The increased resting energy expenditure that is needed in CHF patients to maintain the $Na^+/K^+$ gradient might be assessed with indirect calorimetry or 18F-FDG PET scanning. However, to our knowledge, no such studies have been conducted in potassium depleted patients. Since the effect of angiotensin and aldosterone inhibition have not been directly tested on skeletal muscle preservation and function, this should also be further studied.

## IMPLICATIONS

This hypothesis not only provides an explanation of the beneficial effect of angiotensin and aldosterone inhibitors on muscle mass, but also provides logic behind an useful medication.

ACE-inhibitors, ARBs and MRAs might also be beneficial in other patient groups, for example other chronic diseases leading to cachexia, older patients and critically ill patients. As our society ages, the prevalence of chronic diseases will rise. This makes cachexia a major public health problem, requiring treatments that minimize muscle wasting.

Monitoring potassium balances is an easy and reliable way to monitor skeletal muscle loss and thereby possible effectiveness of treatment. We therefore propose that future CHF studies should address potassium balances together with monitoring of muscle mass.

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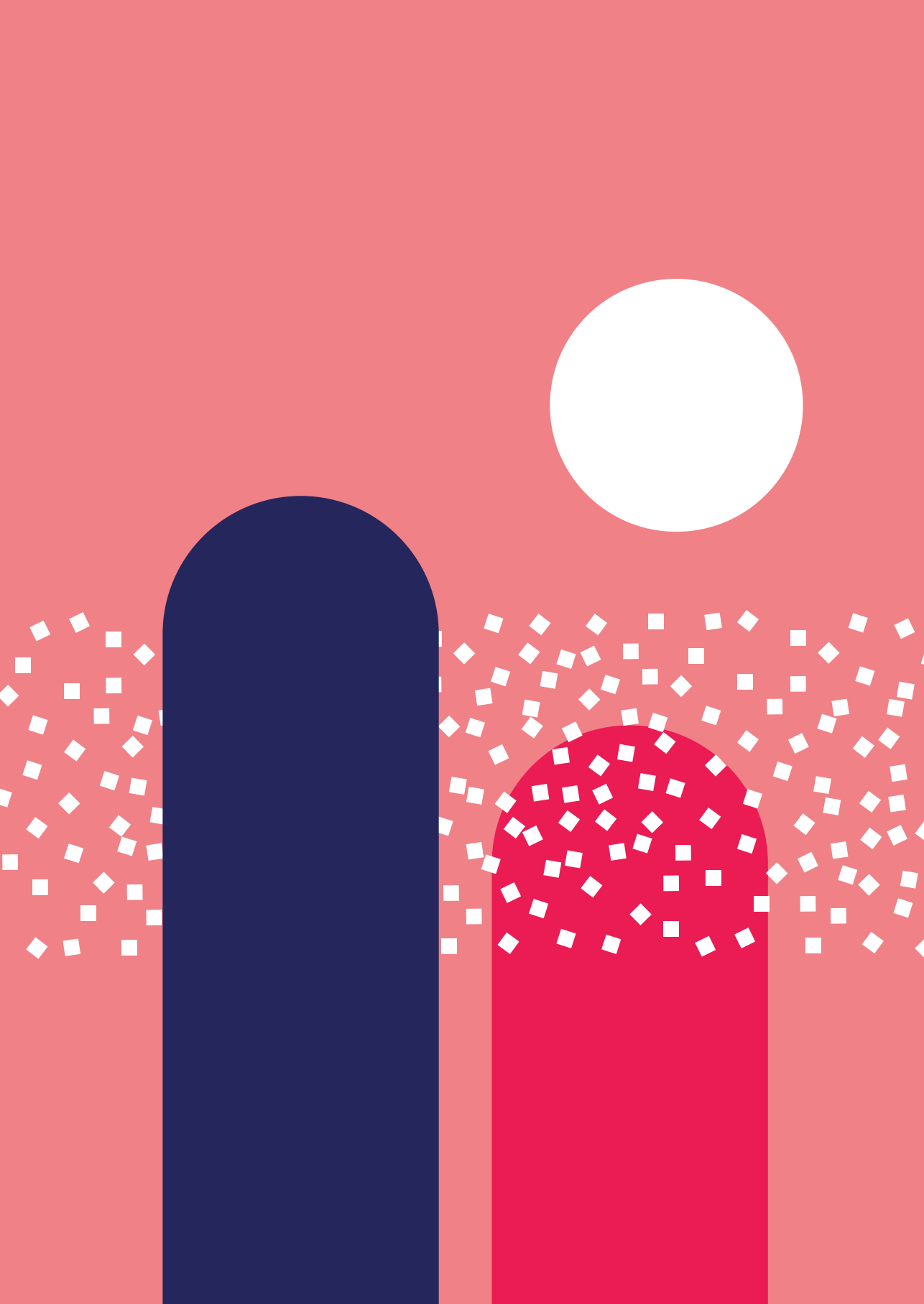

# CHAPTER 7

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## LONG-TERM CHANGES IN DYSNATREMIA INCIDENCE IN THE ICU: A SHIFT FROM HYPONATREMIA TO HYPERNATREMIA

**Annals of Intensive Care 2016;6(1):22**

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## ABSTRACT

### BACKGROUND

Dysnatremia is associated with adverse outcome in critically ill patients. Changes in patients or treatment strategies may have affected the incidence of dysnatremia over time. We investigated long term-changes in the incidence of dysnatremia and analyzed its association with mortality.

### METHODS

Over a 21-year period (1992-2012), all serum sodium measurements were analyzed retrospectively in two university hospital ICUs, up to day 28 of ICU admission for the presence of dysnatremia. The study period was divided into five periods. All serum sodium measurements were collected from the electronic databases of both ICUs. Serum sodium was measured at the clinical chemistry departments using standard methods. All sodium measurements were categorized in the following categories: <120, 120-124, 125-129, 130-134, 135-139, 140-145, 146-150, 151-155, 156-160, >160 mmol/L. Mortality was determined at 90 days after ICU-admission.

### RESULTS

In 80,571 ICU patients 913, 272 serum sodium measurements were analyzed. A striking shift in the pattern of ICU-acquired dysnatremias was observed: the incidence of hyponatremia almost halved (47-25%, $P < 0.001$), whereas the incidence of hypernatremia nearly doubled (13- 24%, $P < 0.001$). Most hypernatremias developed after ICU admission, and the incidence of severe hypernatremia (sodium >155 mmol/L) increased dramatically over the years. On ICU day 10 this incidence was 0.7% in the 1992-1996 period, compared to 6.3% in the 2009-2012 period ($P < 0.001$). More severe dysnatremia was associated with significantly higher mortality throughout the 21-year study period ($P < 0.001$).

### CONCLUSIONS

In two large Dutch cohorts we observed a marked shift in the incidence of dysnatremia from hyponatremia to hypernatremia over two decades. As hypernatremia was mostly ICU-acquired, this strongly suggests changes in treatment as underlying causes. This shift may be related to the increased use of sodium-containing infusions, diuretics and hydrocortisone. As ICU-acquired hypernatremia is largely iatrogenic, it should be – to an important extent – preventable, and its incidence may be considered as an indicator of quality of care. Strategies to prevent hypernatremia deserve more emphasis; therefore we recommend that further study should be focused on interventions to prevent the occurrence of dysnatremias during ICU stay.

## BACKGROUND

Deranged plasma sodium concentrations expose all cells to hypotonic or hypertonic stress. Clinical manifestations of dysnatremia are primarily neurological and rapid changes in plasma sodium in either direction can cause severe, permanent and sometimes even lethal brain injury [1]. The reported prevalence of dysnatremia in the intensive care unit (ICU) ranges between 6.9 and 17.7% and varies according to the time of onset (i.e., on admission or later during ICU stay), the threshold for diagnosis, and the population being assessed [2].

Patients in the ICU are at risk of developing both hyponatremia and hypernatremia. Critical illness may result in increased or reduced activity of the antidiuretic hormone [3,4]. Additional factors that predispose to hypernatremia include a reduced urinary concentrating ability, the inability to express thirst, no free access to water, and increased insensible losses [5, 6]. In addition to critical illness per se, factors contributing to hyponatremia include excess use of hypotonic fluids and drugs stimulating antidiuretic hormone secretion [7].

The severity of hyponatremia on ICU admission is a demonstrated predictor of mortality [8]. Even slightly abnormal sodium levels on ICU admission are independently associated with poor outcome [2,9]. Although ICU-acquired hyponatremia is less prevalent, it is also associated with an increased risk of hospital mortality [5]. ICU-acquired hypernatremia is also an independent risk factor for mortality and associated with increased ICU length of stay [10-13]. The relation between sodium derangement and mortality has been reported in medical, surgical, mixed, cardiac, cardiovascular surgery, trauma, and neurological ICUs [5, 10-15]. Finally, comparable to variability in serum glucose [16] or potassium [17], the magnitude of changes in sodium has also been associated with a higher risk of death in ICU patients [14, 15].

Based on our impression that hypernatremia has nowadays become more prevalent than hyponatremia in the ICU, we hypothesized that a shift in the incidence of hyponatremia and hypernatremia occurred during the past two decades. Therefore, the aim of this study was to analyze the long term changes in the incidences of hyponatremia and hypernatremia in the ICU. Furthermore, we studied the association between dysnatremia and mortality.

## PATIENTS AND METHODS

This retrospective study was performed in two cohorts of adult ICU patients obtained from the two largest ICUs in The Netherlands, including the University Medical Center Groningen (44 bed unit) and the Erasmus Medical Center (48 bed unit). From the ICU of the University Medical Center in Groningen, all patients admitted between 1992 and 2011 were analyzed, and from the ICU of the Erasmus Medical Center in Rotterdam all patients admitted between 1998 and 2012 were analyzed. The 21-year study period was divided into five periods to detect shift in time: 1992-1996, 1997-2000, 2001-2004, 2005-2008, and 2009-2012. Data on the type of admission (surgical, medical, etc.) were available for patients from Groningen but not from Rotterdam. Patients aged < 15 years were excluded. Mortality was determined at 90 days after ICU-admission.

**Table 1. Type of ICU admissions in Groningen in the five time periods**

| | 1992-1996 (n=11,831) | 1997-2000 (n=8,875) | 2001-2004 (n=8,078) | 2005-2008 (n=8,378) | 2009-2011 (n=6,857) | Total (n=44,019) |
|---|---|---|---|---|---|---|
| Admission via emergency department | 19% | 12% | 15% | 16% | 18% | 16% |
| Vascular, abdominal and other surgery | 14% | 17% | 20% | 21% | 21% | 18% |
| Neurosurgery | 11% | 10% | 12% | 14% | 13% | 12% |
| Transplant | 2% | 2% | 2% | 2% | 1% | 2% |
| Cardiothoracic surgery | 51% | 48% | 42% | 41% | 42% | 45% |
| Trauma | 4% | 4% | 5% | 5% | 5% | 4% |
| Medical and miscellaneous | 20% | 19% | 18% | 18% | 17% | 18% |

The anonymized data analysis in this study was performed in accordance with the guidelines and Dutch legislation, and it was approved by the medical ethical committees of our institutions (Medisch Ethische Commissie, UMC Groningen, METc 2014.264, MEC Erasmus MC MEC-2015-401). Since this concerned a retrospective study on routinely collected data, informed consent was not required by the ethical committees.

## SERUM SODIUM MEASUREMENTS

All serum sodium measurements during ICU admission until day 28 were collected from the electronic databases of both ICUs. Serum sodium was measured at the clinical chemistry departments using standard methods (with a pre-analytic dilution, assuming a standard 7% solid phase) or at the ICU with Radiometer 700 series blood gas analyzers with an ion-selective method, that uses no predilution. All sodium measurements (reference range 135-145 mmol/L) were categorized as follows: <120, 120-124, 125-129, 130-134, 135-139, 140-145, 146-150, 151-155, 156-160, >160 mmol/L. The so-called soccer-field plots were generated for the 1992-1996 and the 2009-2012 periods to display the relation between ICU day and the relative incidence of dysnatremia in all patients between ICU day 1 and 28. This way of presentation facilitates easier identification of trends in dysnatremia during the ICU stay. In these plots, dysnatremia was categorized into similar groups as defined earlier.

## PHARMACY DATA

The hospital pharmacy of the University Medical Center in Groningen provided a list of all infusions that were administered in the ICU over the period 1997 through 2011. In addition to the total volume infused, the mean sodium-content was also calculated.

## STATISTICAL ANALYSIS

Comparisons between means and medians were made with the Student's *t*-test and Mann-Whitney *U*-test, respectively. Distributions were compared with the chi-square test. Data are expressed as means with standard deviations. A $P$ value <0.05 was considered statistically significant. Bonferroni correction was used where appropriate. Statistical analysis was performed with SPSS (IBM, version 22).

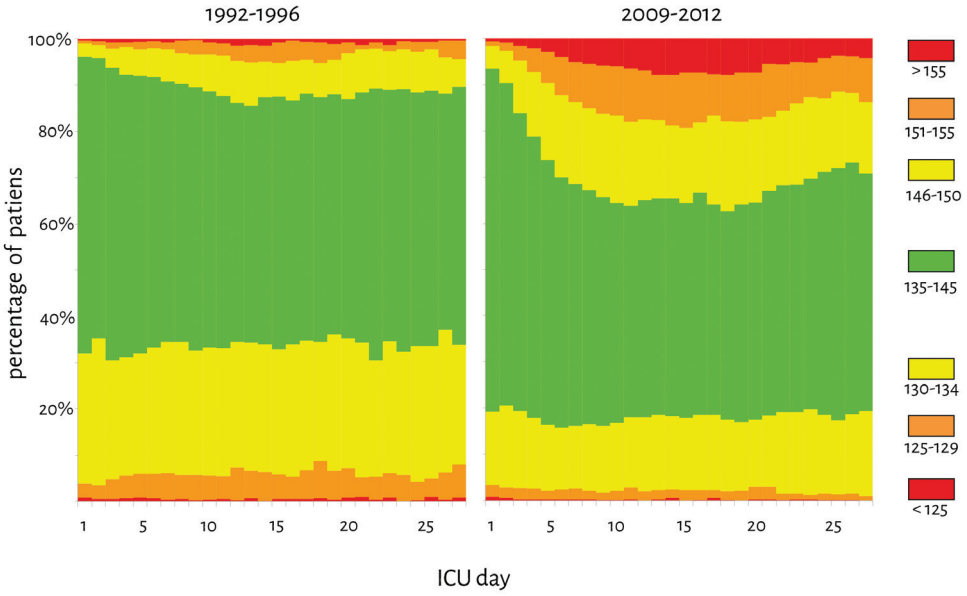


**Figure 1. Time course of sodium derangements.**

Comparison of the development of hyponatremia and hypernatremia between the periods 1992-1996 and 2009-2012. Sodium levels within the reference range are shown in green and progressively more marked derangements in yellow, orange and red, respectively.

# RESULTS

## PATIENT CHARACTERISTICS

In the two centers 80,571 consecutively admitted ICU patients were included, in whom a total of 913,272 serum sodium measurements were performed (55% from Groningen). Sixty-four% of patients were male; mean age was 60 ±16 years, with a mean of 11 ±20 serum sodium measurements/patient. Table 1 shows the type of ICU-admissions in Groningen over time. The case mix of patients remained relatively stable over the study-period, except for a small increase in vascular and abdominal surgery, and a small decrease in cardiothoracic surgery. In the additional data file the data selection (Supplementary material; Figure S1) and the frequency distribution of the number of admitted patients as a function of ICU-day (Supplementary material: Figure S2) are provided.

## LONG TERM CHANGES IN DYSNATREMIA

Figure 1 shows the change in distribution of serum sodium categories during ICU-admission for the first time period (1992 – 1996, left panel) and the last time-period (2009 – 2012, right panel). The figure clearly shows that hyponatremia was more common in the first period, and that hypernatremia became more common in the last period. The figure also shows that in particular the incidence of hypernatremia increased during ICU admission (most notably in the first two weeks) and remained stable until day 20. On ICU day 10, for example, the incidence of hypernatremia >155 mmol/L rose from 0.7% in 1992-1996 to 6.3% in 2009-2012 ($P < 0.001$). Figure 2 shows a different

graphical representation of the incidences of hyponatremia and hypernatremia during the five subsequent time-periods. From this analysis, the decreasing prevalence of hyponatremia and the increasing incidence of hypernatremia are also clearly visible for the five consecutive time periods. For example, the incidence of hyponatremia <130 mmol/L decreased from 47 to 25% ($P < 0.001$) from the first time period (1992-1996) to the last time period (2009-2012), whereas the incidence of hypernatremia >150 mmol/L increased from 13 to 24% ($P < 0.001$) in the same time periods. Over time the use of ion-selective sodium measurements has increased with the implementation of ICU based point-of-care systems from 56 to 79% ($P < 0.001$) in Groningen (Supplementary material: Table S1). However the sodium levels determined by the ion-selective assay were 1.5 mmol/L ($P < 0.001$) lower in the Groningen ICU patients. As the ion-selective sodium levels were lower while being used more frequently, this should not have contributed to the observed trend towards higher sodium levels. Although a clear difference in albumin levels and in particular glucose levels was observed between 1992-1996 and 2009-2011 their statistical relation with sodium levels was very limited (Supplementary material: Figures S5, S6 and Tables S5, S6.).

When the changes in incidence of sodium abnormalities were analyzed separately for the Groningen and Rotterdam ICU's (Supplementary material: Table S3, Figure S3), both ICU's showed a trend towards hypernatremia. When analysis was performed for patients with hypernatremia >150 mmol/L, all subgroups except transplantation showed a trend towards hypernatremia in recent cohorts.

For the Groningen ICU, we also performed similar analyses for the top 35 routine laboratory measurements that were most frequently performed. With the exception of chloride, albumin, haemoglobin, and glucose, no important shifts over time were observed (Supplementary material: Figures S4, S5, S6). From the 1997-2000 to the 2009-2011 period, the mean sodium concentration of the infused fluids in the Groningen ICU increased from 100 to 107 mmol/L ($P < 0.001$; Supplementary material Table S2).

## MORTALITY

Figure 3 shows the mortality rates with the various serum sodium categories and time-periods. Dysnatremia was strongly associated with mortality and showed a U-shaped relationship. Figure 3 demonstrates that this relationship between dysnatremia and mortality remained largely unchanged over the 21-year study period. The overall mortality rose slightly from 13% in 1992-1996 to 15% in 1997-2000, 16% in 2001-2004, 15% in 2005-2008 and 16% in 2009-2012 ($P < 0.001$).

## DISCUSSION

In this large retrospective dual-center study, we observed a consistent and marked shift in the incidence of dysnatremia from hyponatremia to hypernatremia over a two-decade observation period. The incidence of hyponatremia nearly halved over the study period whereas the incidence of hypernatremia almost doubled. The trend towards higher serum sodium levels was consistently observed in both centers, and seemed to be more important in Groningen center. To our knowledge, this clear shift from hyponatremia to hypernatremia has not been reported before. The increased number of studies that address hypernatremia instead of hyponatremia may reflect increased awareness of this problem in other centers as well [5,9,10,13-15]. Our observation that most hypernatremia typically developed after ICU admission strongly suggests that changes in therapy are involved in this trend.

Although Figure 1 shows that hypernatremia at ICU admission has also increased over time, it is in particular the increase of hypernatremia after ICU admission that is striking. Although we do not have the data to evaluate the etiology of the dysnatremia, we do want to speculate on several factors which might have played a role.

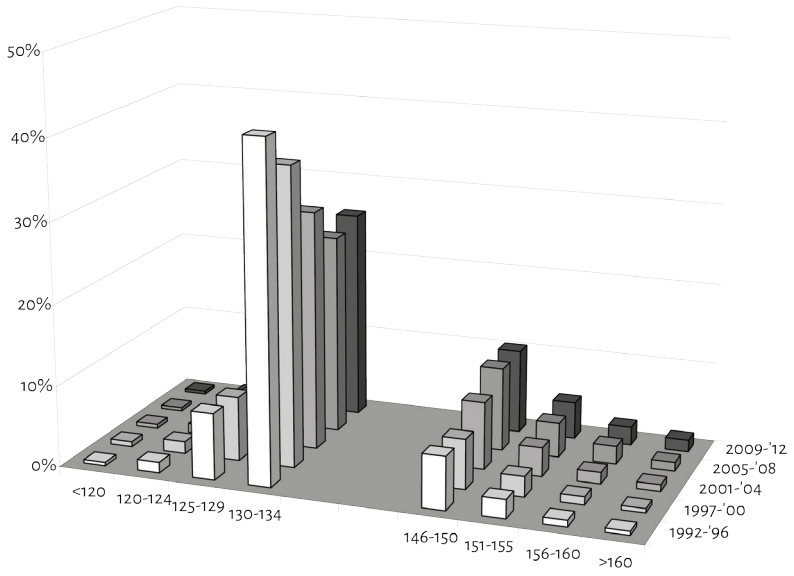


**Figure 2. Incidence of dysnatremia in five time periods.**

For five time periods spanning 1992-2012 the incidence of various degrees in hyponatremia and hypernatremia is shown. Note that for clarity for the two normonatremic categories are not shown.

Two treatment-related factors that may have contributed to the shift from hyponatremia to hypernatremia are the less liberal use of intravenous fluids in combination with wider use of diuretic treatment and the increased use of steroids and in particular hydrocortisone. In 2006 the ARDS clinical network performed a study comparing a conservative strategy (mostly accomplished by administration of furosemide) with a liberal strategy of fluid management in patients with acute lung injury [18]. This trial provided evidence that more restrictive fluid management in critically ill patients results in improved lung function and shortened duration of mechanical ventilation and intensive care stay [19]. Fluid restriction may have contributed indirectly to the rising incidence of hypernatremia. Nevertheless, we have shown previously that more than one third of the patients with ICU-acquired hypernatremia are actually still volume overloaded [11]. This phenomenon is explained by the combination of large volumes of (approximately) isotonic fluids and a reduced urinary concentrating ability. In line with these observations, it was recently shown that NaCl 0.9% used to dilute drugs and keep catheters open contributes to the occurrence of ICU-acquired hypernatremia [20]. In the group of patients with ICU-acquired hypernatremia, the plasma creatinine and dose of furosemide were also higher, again suggesting compromised urinary concentrating ability as an important contributor to hypernatremia.

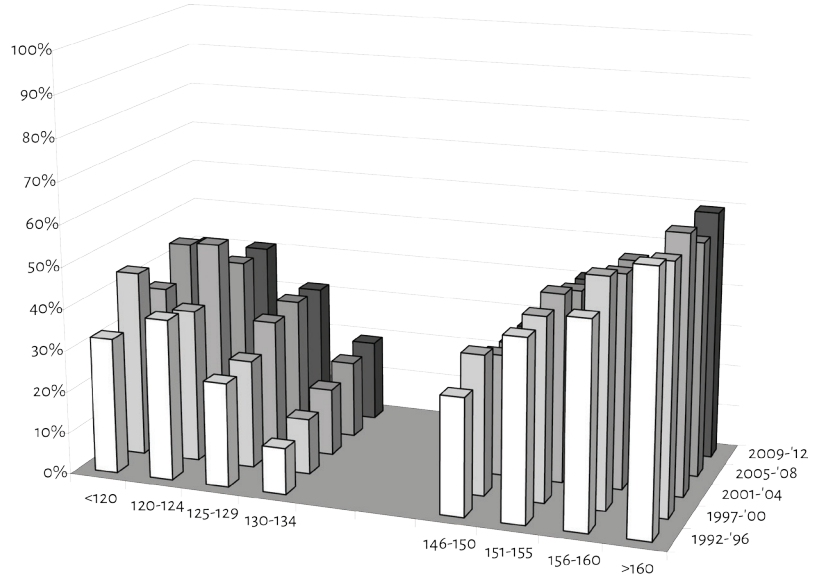


**Figure 3. Dysnatremia and mortality in five time periods.**

Mortality at 90 days shows a U-shaped relation with sodium derangements. Note that the mortality associated with the various dysnatremia categories has not markedly changed over the years.

The role of hydrocortisone in the treatment of septic shock has evolved over the last two decades. In 2002 a French multicenter RCT of patients in vasopressor-unresponsive septic shock showed significant shock reversal and reduction of mortality rate in patients with relative adrenal insufficiency [21]. This led to a more prominent role of hydrocortisone in guidelines for patients with septic shock. In 2008 the CORTICUS-trial, a large European multicenter study

failed to show a mortality benefit with steroid therapy [22]. Nevertheless, a recent study in a university ICU in the Netherlands showed that hydrocortisone was the seventh most frequently administered drug [20]. Even after several systematic analyses, the role of hydrocortisone in septic shock is still not settled [23,24], and a systematic review identified a greater risk of hypernatremia with the use of corticosteroids [23]. We have no data on renal function and the use of renal replacement therapy (RRT) over this period, but RRT did not change in this respect, namely continuous veno-venous hemofiltration with a substitution fluid with a sodium content of 140 mmol/L. The widespread use of dopamine in past decades may have helped to avoid hypernatremia, since dopamine is a natriuretic agent.

The clinical implication of our observations and those of others is that early identification of hypernatremia or preferably impending hypernatremia may help to reduce the incidence, severity, and duration of hypernatremia. It has been proposed to consider the development of hypernatremia during ICU stay as an indicator of quality of care, because ICU patients depend fully on the competence of the medical staff for prescribing fluids and these patients are frequently monitored with sampling of blood [25]. The impact from dysnatremia on morbidity and mortality leads to extensive burden on healthcare resources [26]. It is sobering to note that this proposal to prevent hypernatremia [25] was made more than 15 years ago, and yet its incidence has only increased. Nevertheless, we still believe it may be possible to achieve the best of both worlds, i.e., combine the low hypernatremia levels observed in the 1990s and the low hyponatremia levels observed today. Since hypernatremia is a condition that takes several days to develop and also takes a relatively long time to correct (Figure 1) prevention would be the most desirable strategy. Our own data (Supplementary material: Table S2) show that although the total infused volume decreased, unfortunately the sodium concentration of infused fluids has only increased over the years. A strategy of timely administration of infusion fluids with lower sodium content in the face of imminent hypernatremia seems reasonable to pursue. In this regard, the trend to use balanced fluids with lower sodium concentrations than the 154 mmol/L in NaCl 0.9% may help [27,28]. Since patients more often arrive at the ICU with hypernatremia, this is also relevant for the emergency department and operating room. When other risk factors for hypernatremia such as the administration of furosemide [20] or hydrocortisone are present, an even earlier switch to infusions with minimal sodium concentrations may be desirable. Monitoring of sodium concentrations is facilitated with modern point-of-care equipment. In the slipstream of glucose control, we have demonstrated that careful computer guided potassium control is feasible with a clear reduction of abnormal potassium levels [17]. In fact, integration of potassium regulation with glucose control was very effective with marginal extra costs or time spent [29]. But implementing computerized sodium control will be considerably more challenging since more variables have to be taken into account. Although no study has shown that treatment of dysnatremia reduces mortality, a large multicenter observational study recently showed that successful rapid correction of dysnatremia was independently associated with survival [30]. The 28-day mortality in patients whose dysnatremia was corrected within 48 hours was not significantly different from that in patients with normal serum sodium concentrations on ICU admission [30]. This finding suggests that the association between dysnatremia and mortality may be causal and could be improved by timely correction, although conclusive evidence should come from a randomized trial.

This study has a number of limitations. First, the identified trends in our two ICUs (large ICUs in university hospitals in the Netherlands) may not apply to other types of ICUs. Second, in addition to treatment-related factors, patient-related factors may also have played a role. For example, admissions for traumatic brain injury may have changed over the years, but this was not clearly reflected in our analysis of type of ICU admissions (Table 1). Also hypernatremia in patients with severe traumatic brain injury typically develops within the first three days [31] and not at the considerably later time as shown in Figure 1. We do not have the data on shifts in medication usage in our two centers to support our speculation on the etiology of the dysnatremia. Data on sodium concentration in mmol/L of the administered infusions in the Groningen ICU show a significant increase over time (Supplementary material: Table S2). Data on hyperosmolar dye contrast administration, the use of citrate anticoagulation on RRT or (par) enteral nutrition were also not analyzed. We were also not able to identify complications of dysnatremia. Likewise we could not reliably determine how often a disastrous complication such as central pontine myelinolysis occurred [32]. Finally, historical comparisons are vulnerable to all kinds of system changes that inevitably happen over time. This may be the case for sodium measurement. One study showed that the discrepancy between the direct assay and the indirect assay (which includes a dilution step) became larger as plasma albumin decreased [33, 34]. Because patients in the ICU are often hypoalbuminemic, this may predispose to pseudohypernatremia. However, the point-of-care measurements that use a direct sodium assay became more prevalent during the study-period. Thus, pseudohypernatremia may have been more common in the past, making the incidence of true hypernatremia in earlier time-periods even lower.

## CONCLUSIONS

In two large cohorts of ICU patients, we found a shift in the incidence of dysnatremias. The incidence of hyponatremia decreased over the study period, whereas the incidence of hypernatremia increased. We suggest this shift is related to the increased use of diuretics and hydrocortisone. As ICU-acquired hypernatremia is often iatrogenic it thus may be – to an important extent – preventable, and its incidence may be considered as a quality indicator. The relation of dysnatremia with mortality remained unchanged over the 21-year study period; therefore we recommend that further study should be focused on interventions to prevent the occurrence of dysnatremias during ICU stay.

## ACKNOWLEDGEMENTS

We thank dr. W. Bult, Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, the Netherlands for supplying the data of the administered infusion fluids in the UMCG.

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LONG-TERM CHANGES IN DYSNATREMIA INCIDENCE IN THE ICU: A SHIFT FROM HYPONATREMIA TO HYPERNATREMIA

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# CHAPTER 7

Supplementary material

# TABLES

**Table S1. Changes in (relative) use of ion-selective sodium measurements in the Groningen ICU and the associated sodium concentrations measured**

| Epoch | Number | Percentage of assays that is ion-selective | Mean ±SD [$Na^+$] with conventional assay mmol/L | Mean ±SD [$Na^+$] with ion-selective assay mmol/L |
|---|---|---|---|---|
| 1992-'96 | 85918 | 56% | 138.3 ±6.0 | 136.6 ±4.0 |
| 1997-'00 | 66848 | 54% | 138.1 ±6.1 | 136.2 ±4.3 |
| 2001-'04 | 71570 | 52% | 140.3 ±6.9 | 136.9 ±4.7 |
| 2005-'08 | 136304 | 67% | 141.6 ±6.2 | 139.6 ±5.5 |
| 2009-'12 | 172506 | 79% | 142.3 ±6.1 | 139.9 ±5.8 |
| Total | 533146 | 66% | 140.2 ±6.5 | 138.7 ±5.5 |

Over time the use of ion-selective sodium measurements has increased with the implementation of ICU-based point-of-care systems from 56% to 79% ($P < 0.001$) in Groningen. The sodium levels reported by the ion-selective assay are 1.5 mmol/L ($P < 0.001$) lower in the Groningen ICU patients. The sodium levels of the Rotterdam ICU were not split, since this ICU has used conventional assays throughout the study period. As the ion-selective sodium levels were lower whilst being used more frequently, this should not have contributed to the observed trend towards higher sodium levels.

**Table S2. Bulk infusion fluid use**

| Epoch | Sodium (mol) | Volume (L) | Concentration (mmol/L) |
|---|---|---|---|
| 1992-1996 | NA | NA | NA |
| 1997-2000 | 11,895 | 119,152 | 99.8 |
| 2001-2004 | 12,571 | 119,443 | 105.2 |
| 2005-2008 | 13,676 | 127,908 | 106.9 |
| 2009-2011 | 10,987 | 102,837 | 106.8 |

All infusions administered in the Groningen ICU per epoch, obtained from hospital pharmacy data. When the change in mean sodium concentration of all infusions was determined, a rise of 7% was observed ($P < 0.001$). NA, not available

**Table S3A. Incidence of sodium abnormalities over time in Groningen ICU**

| | <120 | 120-124 | 125-129 | 130-134 | 146-150 | 151-155 | 156-160 | >160 | N |
|---|---|---|---|---|---|---|---|---|---|
| **1992-'96** | 0.4% | 1.3% | 8.2% | 41.7% | 6.6% | 2.3% | 0.8% | 0.5% | 10925 |
| **1997-'00** | 0.4% | 1.4% | 8.8% | 43.4% | 5.3% | 2.2% | 0.9% | 0.5% | 8679 |
| **2001-'04** | 0.3% | 1.0% | 6.2% | 34.9% | 7.6% | 3.4% | 1.6% | 1.2% | 8152 |
| **2005-'08** | 0.2% | 0.6% | 3.8% | 24.5% | 11.3% | 4.8% | 2.4% | 1.2% | 8832 |
| **2009-'12** | 0.3% | 0.8% | 4.2% | 27.3% | 12.4% | 5.4% | 2.8% | 1.2% | 7535 |

**Table S3B. Incidence of sodium abnormalities over time in Rotterdam ICU**

| | <120 | 120-124 | 125-129 | 130-134 | 146-150 | 151-155 | 156-160 | >160 | N |
|---|---|---|---|---|---|---|---|---|---|
| **1992-'96** | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **1997-'00** | 1.0% | 1.7% | 6.3% | 24.7% | 7.8% | 3.1% | 1.2% | 0.5% | 4645 |
| **2001-'04** | 0.7% | 1.3% | 6.2% | 24.5% | 9.0% | 3.8% | 1.3% | 0.5% | 8434 |
| **2005-'08** | 0.5% | 1.1% | 5.3% | 24.8% | 9.6% | 3.8% | 2.1% | 1.0% | 11197 |
| **2009-'12** | 0.5% | 1.0% | 4.9% | 24.8% | 9.2% | 4.1% | 1.9% | 1.6% | 12326 |

Distribution of epoch-dependent sodium-abnormalities for the two ICU's. For each patient the most extreme sodium abnormality in either direction was recorded. N is number of patients per epoch; NA, not available.

**Table S4. Type of ICU admissions and incidence of hypernatremia >150 mmol/L**

| | 1992-'96 | 1997-'00 | 2001-'04 | 2005-'08 | 2009-'11 |
|---|---|---|---|---|---|
| **Medical** | 109 (8.7%) | 52 (8.2%) | 111 (17.5%) | 120 (18.2%) | 106 (21.7%) |
| **Vascular, abdominal, miscellaneous** | 68 (4.4%) | 65 (4.4%) | 102 (6.5%) | 185 (10.1%) | 153 (9.5%) |
| **Neurosurgery** | 53 (4.6%) | 30 (3.3%) | 55 (5.6%) | 105 (8.5%) | 71 (7.2%) |
| **Transplantation** | 42 (23.1%) | 17 (10.0%) | 13 (8.1%) | 25 (12.7%) | 16 (12.6%) |
| **Cardiothoracic surgery** | 64 (5.5%) | 70 (1.7%) | 65 (1.9%) | 127 (3.5%) | 163 (5.2%) |
| **Trauma** | 23 (5.5%) | 20 (5.5%) | 49 (12.6%) | 70 (17.8%) | 76 (21.1%) |

Numbers of ICU patients with hypernatremia over 150 mmol/L at any time point during ICU stay in Groningen ICU. For all categories except transplantation. a clear increase ($P < 0.001$) in the incidence of hypernatremia is observed.

**Table S5. Linear regression model with median daily sodium as dependent variable for all ICU days**

| | B (95% CI) | *P* |
|---|---|---|
| Constant | 138 | |
| ICU day | 0.31 (0.30;0.33) | <0.001 |
| $(ICU\ day)^2$ | -0.11 (-0.12;-0.10) | <0.001 |
| Albumin | -0.31 (-0.34;-0.27) | <0.001 |
| Glucose | -0.054 (-0.065;-0.043) | <0.001 |

For 149,000 ICU days albumin, sodium and glucose levels were available for the Groningen ICU. This model includes ICU-day. A mild inverse relation between glucose (in mmol/L) and sodium was observed. Thus a 10 mmol/L increase in glucose (180 mg/dL) is associated with a decrease of 0.5 mmol/L in sodium. Likewise a 10 g/L decrease in albumin was associated with a 0.3 mmol/L rise in sodium.

**Table S6. Linear regression model with median daily sodium as dependent variable on ICU day 1**

| | B (95% CI) | *P* |
|---|---|---|
| Constant | 137 | |
| Albumin | -0.019 (0.011;0.027) | 0.001 |
| Glucose | -0.005 (-0.025;0.016) | 0.67 |

For 17,039 patients sodium, glucose and albumin were available on the date of ICU-admission. Only albumin has a slight relation with sodium levels.

## FIGURES

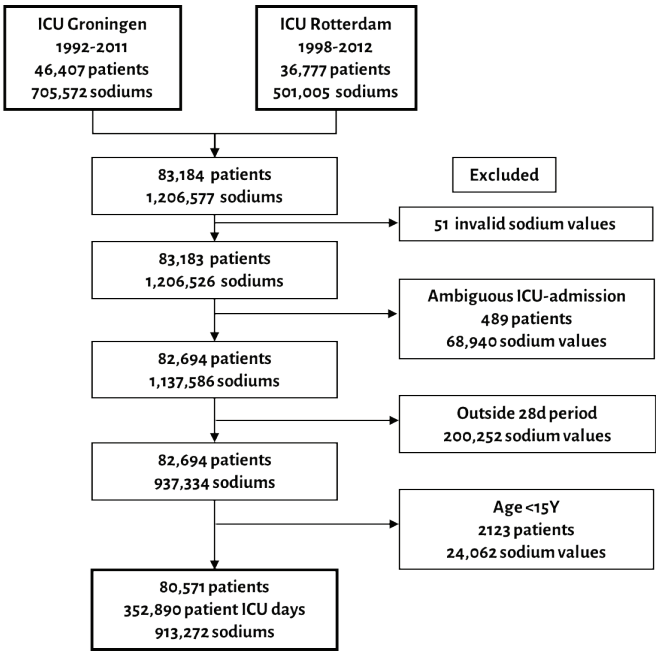



**Figure S1. Flowchart patient and data selection.**

Depiction of the various data reduction steps that resulted in the selection of the 80,571 patients from the Groningen ICU and Rotterdam ICU. Invalid values, values from children, values obtained outside the ICU and data from later than 28 days were excluded.

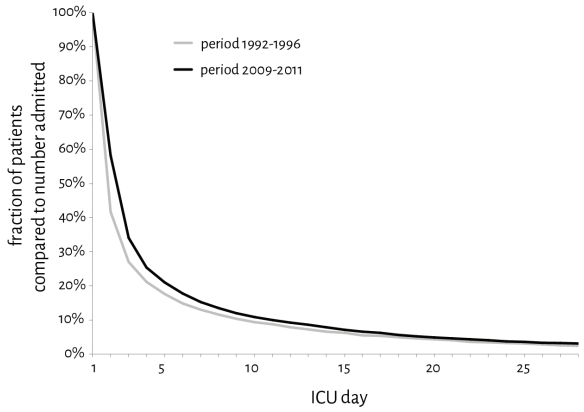



**Figure S2. Fraction of patients over time.**

This study examined sodium levels up to 28 days after ICU admission. As a reference. these curves show the number of patients that are still admitted at the Groningen ICU over time.

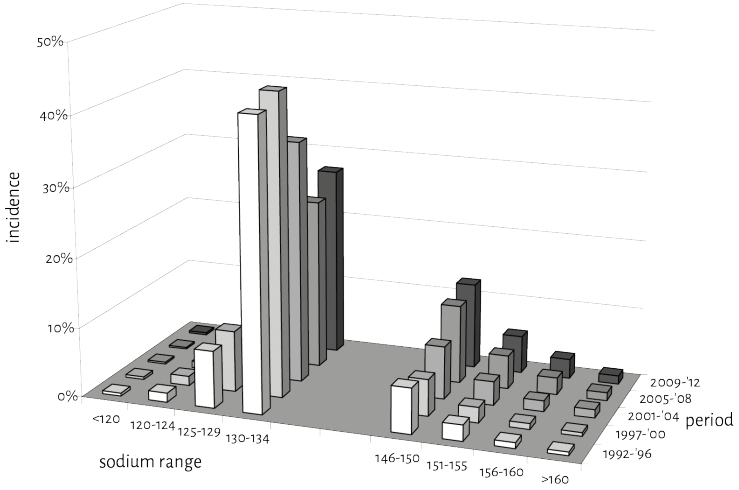



**Figure S3. Incidence of dysnatremia in five time periods for Groningen only.**

For five time periods spanning 1992 to 2012 the incidence of various degrees of hyponatremia and hypernatremia are shown for the Groningen ICU only. When compared with Figure2 that shows the combined incidence of the Groningen and Rotterdam ICU's the same pattern of an increase of hypernatremia and in particular of marked hypernatremia. Note that for clarity the two normonatremic categories are not shown. Underlying data are shown in table

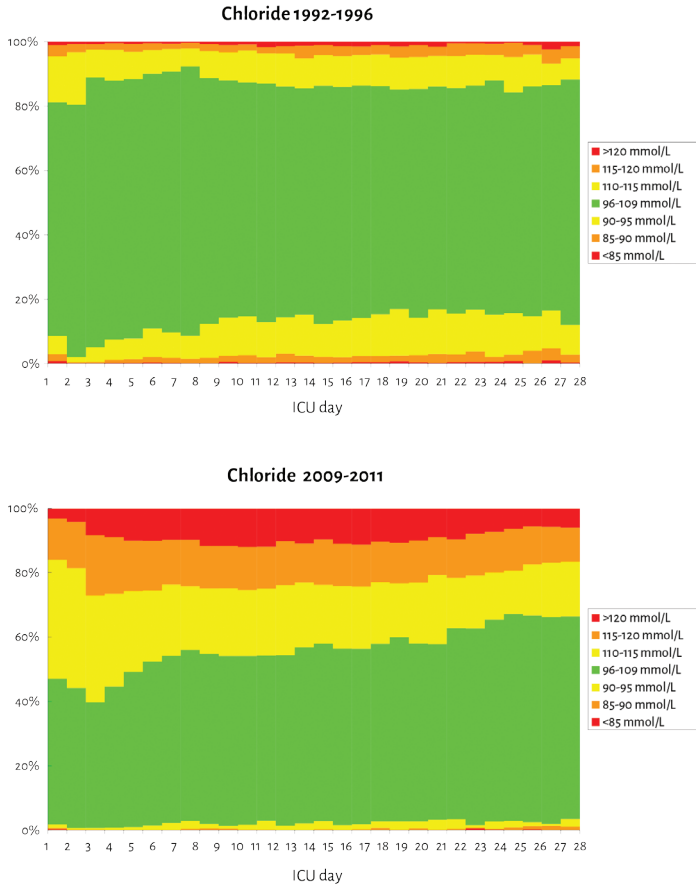



**Figure S4. Soccerfield plots of chloride abnormalities in 1992-'96 and 2009-'11.**

For each day in the Groningen ICU for each patient the median chloride value was determined. The distribution of all these values is color-coded with the reference range in green. Note that during the later epoch higher chloride levels develop after ICU-admission. Note the strong similarity with the same type of plot for sodium. suggesting NaCl administration as a common cause.

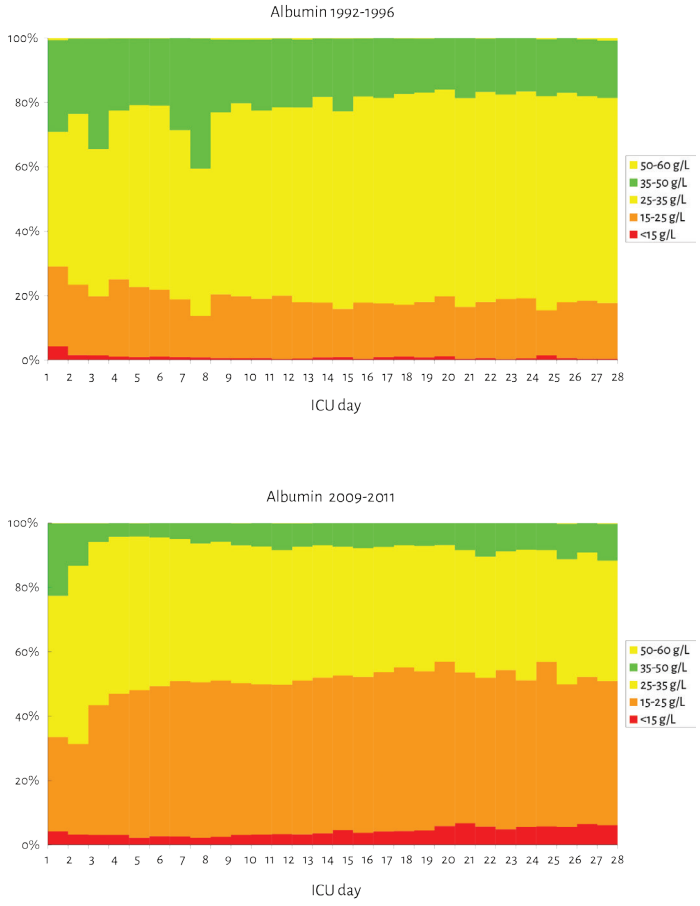



**Figure S5. Soccerfield plots of albumin abnormalities in 1992-'96 and 2009-'11.**
For each ICU in the Groningen ICU for each patient the median albumin value was determined. The distribution of all these values is color-coded with the reference range in green. Note how in the more recent epoch much more deranged albumin levels are observed (and accepted).

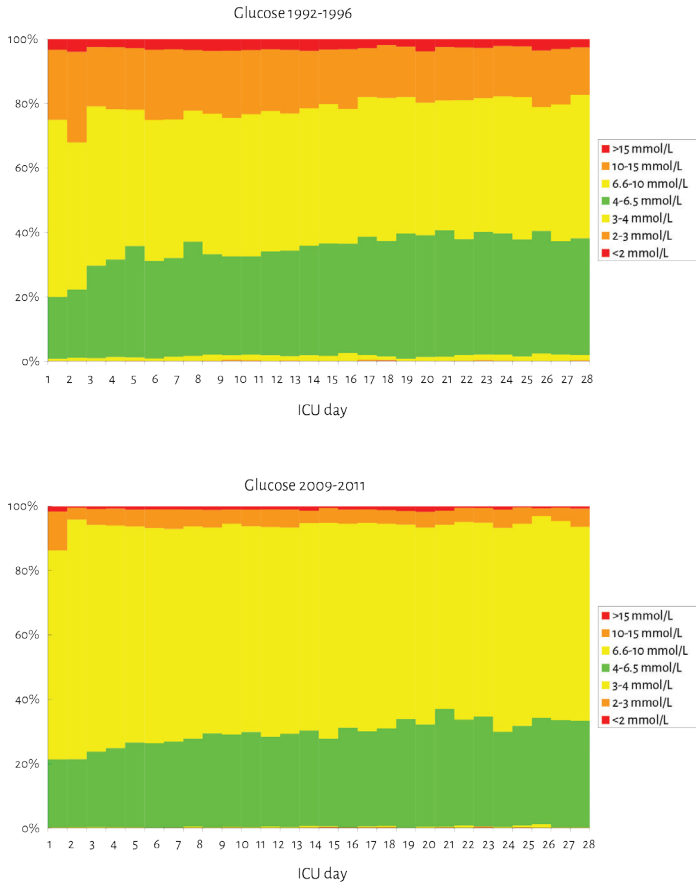
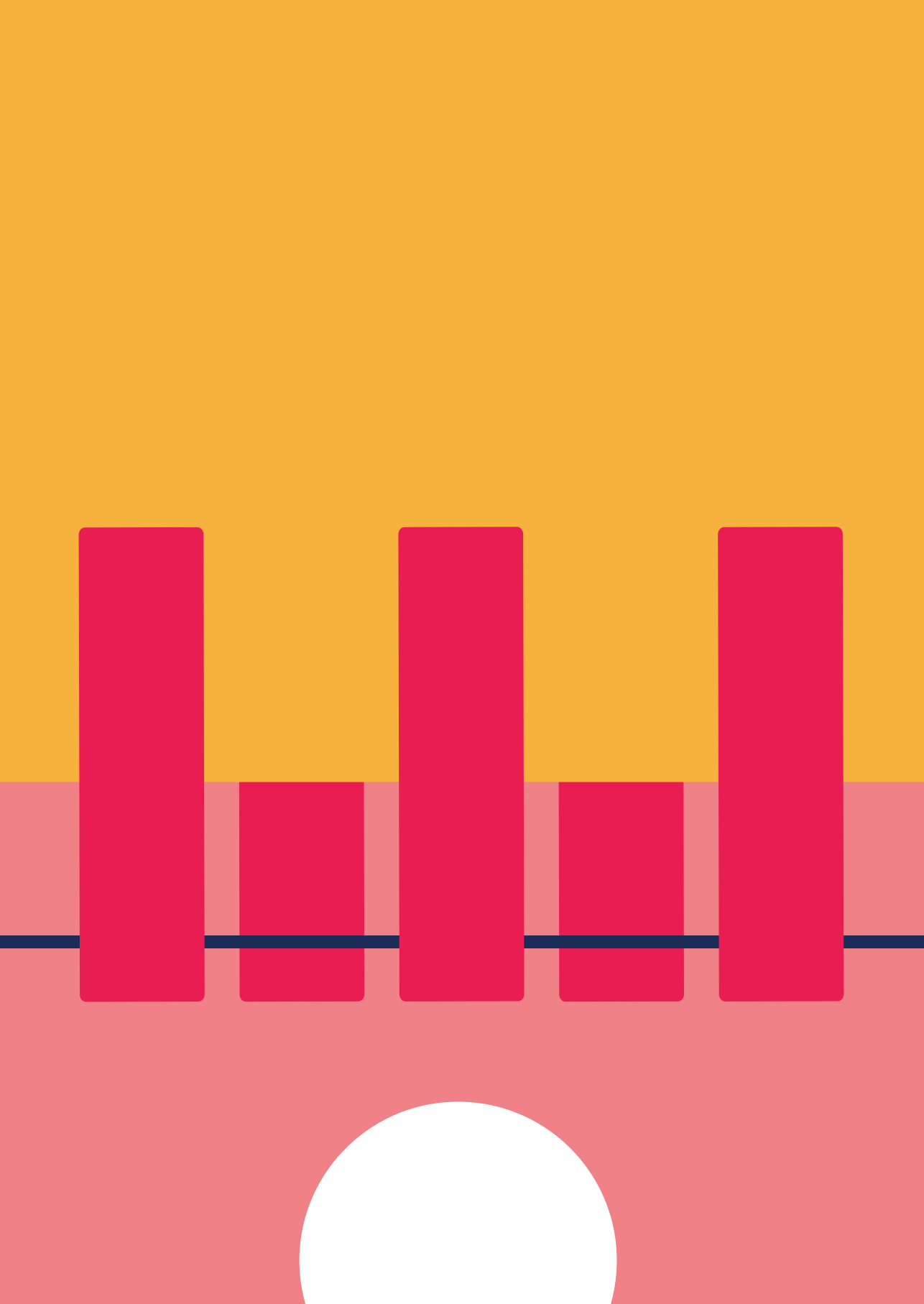



**Figure S6. Soccerfield plots of glucose abnormalities in 1992-'96 and 2009-'11.**

Example of medical policy-related change in laboratory value over time. For each day in the Groningen ICU for each patient the median glucose value was determined. The distribution of all these values is color-coded with the reference range in green. Note that during the later epoch glucose levels are better regulated. not as a result of changes in case mix. but as a result of active glucose control.



# CHAPTER 8

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# ESTIMATION OF SODIUM AND CHLORIDE STORAGE IN CRITICALLY ILL PATIENTS: A BALANCE STUDY

**Annals of Intensive Care 2018;8(1):97.**

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## ABSTRACT

### BACKGROUND

Non-osmotic sodium storage has been reported in animals, healthy individuals and patients with hypertension, hyperaldosteronism and end-stage kidney disease. Sodium storage has not been studied in ICU patients, who frequently receive large amounts of sodium chloride containing fluids. The objective of our study was to estimate sodium that cannot be accounted for by balance studies in critically ill patients. Chloride was also studied. We used multiple scenarios and assumptions for estimating sodium and chloride balances.

### METHODS

We retrospectively analyzed patients admitted to the ICU after cardiothoracic surgery with complete fluid, sodium and chloride balance data for the first 4 days of ICU treatment. Balances were obtained from meticulously recorded data on intake and output.
Missing extracellullar osmotically active sodium (MES) was calculated by subtracting the expected change in plasma sodium from the observed change in plasma sodium derived from balance data. The same method was used to calculate missing chloride (MEC). To address considerable uncertainties on the estimated extracellular volume (ECV) and perspiration rate, various scenarios were used in which the size of the ECV and perspiration were varied.

### RESULTS

A total of 38 patients with 152 consecutive ICU days were analyzed. In our default scenario, we could not account for 296±35 mmol of MES in the first 4 ICU days. The range of observed MES in the five scenarios varied from 111±27 to 566±41 mmol ($P < 0.001$). A cumulative value of 243±46 mmol was calculated for MEC in the default scenario. The range of cumulative MEC was between 62±27 mmol and 471±56 mmol ($P = 0.001$ and $P = 0.003$). MES minus MEC varied from 1±51 mmol to 123±33 mmol in the five scenarios.

### CONCLUSIONS

Our study suggests considerable disappearance of osmotically active sodium in critically ill patients and is the first to also suggest rather similar disappearance of chloride from the extracellular space. Various scenarios for insensible water loss and estimated size for the ECV resulted in considerable MES and MEC, although these estimates showed a large variation. The mechanisms and the tissue compartments responsible for this phenomenon require further investigation.

## BACKGROUND

When long-term balance studies in humans demonstrated that sodium could accumulate without weight gain or hypernatremia, this challenged the generally accepted model on sodium homeostasis [1]. This model states that changes in sodium homeostasis can primarily be explained by a two-compartment model with an intracellular (ICV) and extracellular volume (ECV), where key ions are completely dissolved - i.e., osmotically active. An extra compartment that stores sodium nonosmotically without causing an expansion of the ECV has been proposed by Titze, *et al.* [2]. In both animal and human studies, they found that sodium is stored nonosmotically in the skin [2,3]. Nonosmotic sodium storage is presumably facilitated by large strongly negatively charged polymers such as glycosaminoglycans [4,5]. The accumulation of chloride in the skin has been suggested in an animal model [6,7], but has not been as extensively studied as sodium storage.

Patients admitted to the intensive care unit (ICU) typically receive large amounts of sodium and chloride during their ICU treatment [8]. Both hypernatremia and hyperchloremia are a frequent complication in critically ill patients and are associated with adverse outcome [9-12]. The infusion of high amounts of chloride is also recognized as cause of hyperchloremic acidosis [11,12]. Improved understanding of sodium chloride homeostasis in this patient group is therefore of utmost importance. To our knowledge, no studies have tried to measure missing sodium as evidence of stored sodium in ICU patients. Likewise, a potentially similar phenomenon for chloride has not been studied yet.

The objective of our study was therefore to estimate sodium and chloride that might "disappear" in balance studies in ICU patients. Since random and systematic errors as well as different assumptions on the size of the ECV and perspiration strongly affect the calculated sodium or chloride deficit, five scenarios were tested in which the assumed sizes of the ECV or perspiration were varied.

## MATERIALS AND METHODS

### STUDY DESIGN

This observational retrospective balance study involved all patients of ≥18 years admitted to a tertiary cardiothoracic ICU from October 2010 until December 2014 with a minimal ICU length of stay of 4 days.

### DATA COLLECTION

Data that were collected and analyzed included basic demographics, reason of admission, acute physiology and chronic health evaluation (APACHE-IV) score for disease severity, acute kidney injury according to the KDIGO AKI criteria in the first 7 days and in-hospital mortality [13]. Fluid, sodium and chloride balances were derived from meticulously recorded input records (including enteral and parenteral feeding and administered fluids, including creep fluids such as solvent solutions) and output records, including daily 24-h urine collections. Our ICU did not have a full electronic patient database management system during the study period. Therefore, all data were derived from nursing and medical charts. All electrolyte concentrations, determined in blood or 24h urine, were collected.

**Table 1. Patient characteristics**

| | n= 38 |
|---|---|
| Age,years | 66 (13) |
| Sex, male | 28 (74%) |
| Reason of admission | |
| *Cardiothoracic surgery* | 31 (82%) |
| *Trauma* | 1 (3%) |
| *Vascular surgery* | 1 (3%) |
| *Miscellaneous* | 5 (13%) |
| LOS ICU, d | 7.4 (4.8-13.7) |
| Patients on diuretics | 25 (66%) |
| APACHE-IV | 60 (44-71) |
| Hospital mortality | 4 (11%) |
| AKI | 11 (29%) |
| *Stage 1* | 6 (55%) |
| *Stage 2* | 3 (27%) |
| *Stage 3* | 2 (18%) |

Data are depicted as mean (SD), n (%) or median (interquartile range) as appropiate.
APACHE, Acute Physiology and Chronic Health Evaluation.

## ESTIMATION- (MEC)

Estimation of missing extracellullar osmotically active sodium (MES) and chloride (MEC)
The most important components to determine electrolyte balances are detailed records of fluids, administered to or lost by the patient, including 24-h urine analyses. The detailed calculations used for determining water, sodium and chloride balances, including the estimation for (in)sensible perspiration, have been described earlier and are specified in detail in the supplementary material (Supplementary material: Tables ST1-ST3) [8].

Insensible perspiration was calculated as:

> Insensible perspiration = 10 mL/kg/day + 2.5 mL/kg/day per degree centigrade above 37°C (max body weight in equation 100 kg) ( x 0.6 if intubated )(x 0.5 on admission day) [14]

For insensible perspiration, core temperature measured via the bladder catheter was used.

To estimate MES for each ICU patient we compared the observed changes in estimated extracellular $\Delta Na_{obs}$ with the expected change ($\Delta Na_{exp}$).

Of every ICU calender day, last measured plasma sodium was compared with the last measured plasma sodium of the previous day. For the patients studied, we defined the ECV at 40% in our default model, since surgical patients receive a considerable fluid load perioperatively [15]. We corrected for different sizes of the ECV at the beginning of the day versus the end of day, due to infused fluids.

Only $ECV_{first}$ that was calculated for admission day used measured body weight:

> $ECV_{first}$ = 0.4 x body weight (kg)

The extracellular volume at the end of the day (i.e., 23:59) was defined as:

$$ECV_{23:59} = ECV_{previous} + \text{fluid balance (L)}$$

Where $ECV_{previous}$ is the ECV from 24h earlier, or in the case it concerns the end of the first ICU day it relates to $ECV_{first}$
The extracellular volume at the beginning of the next day (i.e., 00:00) was defined as:

$$ECV_{00:00} = ECV_{\text{last of the previous day}} \text{ (L)}$$

The expected change in total amount of sodium in the ECV over a calender day was defined as:

$$\Delta Na^{+}_{exp} = [Na^{+}]_{last} \times ECV_{last} - [Na^{+}]_{previous} \times ECV_{previous} \text{ (mmol)}$$

The observed change in total extracellular sodium on the basis of administrated and excreted sodium was thereafter defined as:

$$\Delta Na^{+}_{obs} = \text{sodium balance} = Na^{+}_{in} - Na^{+}_{out} \text{ (mmol)}$$

The missing extracellular osmotically active sodium that apparently 'disappeared' from the ECV was defined as:

$$MES = \Delta Na^{+}_{obs} - \Delta Na^{+}_{exp} \text{ (mmol)}$$

For chloride, the same method as described above was used to calcute MEC, where instead of sodium, chloride should be read.

As a sensitivity analysis to test the robustness of our results, we tested 2x2 additional more extreme scenarios with respect to our assumptions on the ECV and perspiration. Where the default model assumed an ECV of 40% of the body weight and an insensible perspiration of 10 ml/kg/day, we tested both an extracelular compartment of 20% of bodyweight [16] and 60% of bodyweight [17]. In order to encapsulate the wide uncertainty in estimating actual perspiration, we also tested both lower and upper published extremes in perspiration rate of 5 ml/kg/day plus 2.5 ml/kg/day per degree centigrade above 37°C and a perspiration rate of 20 ml/kg/day plus 2.5 ml/kg/day per degree centigrade above 37°C.

To assess the differences in ECV between males and females, we performed a sub analysis. In this analysis, an ECV of 40% of the body weight was assumed for males and an ECV of 30% was assumed for females.

## STATISTICAL ANALYSES

Means are given ±SE, medians with interquartile range, unless otherwise indicated. MES and MEC were compared with a Student's *t*-test. A two-sided $P < 0.05$ was considered significant. Cumulative calculations took account of increases in cumulative errors with the Pythagorean theory of error propagation. Balance calculations and statistical analysis were performed with SPSS 23.0 (IBM, Chicago, IL).

# RESULTS

A total of 38 patients with 152 consecutive ICU days were included. Their baseline characteristics are shown in Table 1.

The included patients received large amounts of fluids (13.6±0.6 L), sodium (1441±75 mmol) and chloride (1377±76 mmol) in the 4-day period, resulting in a cumulative fluid balance of 3.9±0.6L, a sodium balance of 822±76 mmol and a chloride balance of 556±82 mmol. Both the mean plasma sodium and chloride concentrations did not significantly change during the first 4 ICU days (Table 2).

## MISSING EXTRACELLULAR OSMOTICALLY ACTIVE SODIUM AND CHLORIDE

Based on our calculations, for sodium a MES of 74±15 mmol per day was observed. This resulted in a cumulative MES of 296±35 mmol during 4 ICU days (Figure 1). For chloride, a MEC of 61±23 mmol per day was seen with a cumulative MEC of 243±46 mmol over the first 4 ICU days (Figure 1).

We also calculated the difference between MES and MEC. The cumulative difference was 56±40 mmol over the first 4 ICU days.

**Table 2. Cumulative data on fluid and electrolyte administration**

| | Day 1 | Day 2 | Day 3 | Day 4 | *P** |
|---|---|---|---|---|---|
| *Intake* | | | | | |
| Fluid, L | 3.6±0.4 | 7.9±0.5 | 11.0±0.5 | 13.6±0.6 | |
| Sodium, mmol | 460±52 | 935±67 | 1235±72 | 1441±75 | |
| Chloride[a], mmol | 420±53 | 872±68 | 1162±79 | 1377±76 | |
| *Output* | | | | | |
| Fluid, L | 1.6±0.1 | 3.9±0.2 | 6.5±0.3 | 8.9±0.3 | |
| Sodium, mmol | 139±14 | 293±23 | 472±30 | 626±35 | |
| Chloride[a], mmol | 117±17 | 255±28 | 418±43 | 574±47 | |
| *Balance* | | | | | |
| Fluid, L | 1.9±0.3 | 3.7±0.5 | 4.0±0.5 | 3.9±0.6 | |
| Sodium, mmol | 321±47 | 642±62 | 769±72 | 822±76 | |
| Chloride[a], mmol | 274±51 | 498±66 | 535±82 | 556±82 | |
| Plasma sodium, mmol/L | 137.1±0.5 | 136.6±0.5 | 136.2±0.6 | 136.9±0.5 | 0.741 |
| Plasma chloride[a], mmol/L | 109.8±0.9 | 109.3±0.8 | 108.2±0.9 | 108.0±0.9 | 0.107 |

Data are depicted as mean ±SE.

*Difference between day 1 and day 4.

[a]Chloride data were available for 27, 7, 24 and 28 patients, respectively, on day 1 to day 4.

## SCENARIOS

In the four scenarios in addition to the default scenario. we changed the assumed ECV and assumed perspiration and assessed their impact on MES and MEC (Figures 2 and 3) .

When perspiration was increased to 20 ml/kg/d, MES doubled for both the 20% and 60% ECV scenario (551±35 mmol and 566±41 mmol respectively, both $P < 0.001$, Figure 2A). After decreasing perspiration to 5 ml/kg/d, in both the ECV of 20% and 60% scenario, the amount of sodium we could not account for decreased more than 2.5 times the initial calculated MES (111±27 mmol and 126±31 mmol, respectively, both $P < 0.001$).

When these four scenarios were repeated for the calculations of MEC, similar results were obtained. When perspiration was increased to 20 ml/kg/d, for both the 20% and 60% ECV scenario we observed a similar increase of MEC from 243±46 mmol to 414±39 mmol ($P = 0.006$) to and 471±56 mmol ($P = 0.003$, Figure 2B). After decreasing perspiration to 5 ml/kg/d, MEC decreased. A MEC of 62±27 mmol was observed when ECV was set at 20% in the low perspiration scenario ($P = 0.001$). However, when ECV was defined as 60%, MEC did not significantly change (243±46 mmol vs. 119±55 mmol, respectively, $P = 0.09$).
For all five depicted scenarios, the difference between MES and MEC was also calculated (Figure 3) to identify potential structural differences between sodium and chloride disappearance. These differences varied from 1±51 mmol to 123±33 mmol, indicating that MES and MEC were of the same order of magnitude.
The sub-analysis to assess sexual differences in ECV can be found in the supplementary material (Supplementary material: Figure SF1).

## DISCUSSION

This is the first balance study that aimed to estimate missing extracellular sodium (MES) in ICU patients and missing extracellular chloride (MEC) in any patient group. Although we found considerable variations in estimated MES and MEC according to the various scenarios the results suggest a considerable MES and a somewhat lower MEC (Figure 3).

To calculate MES and MEC, we used one default and four more extreme scenarios, which we believe cover the scope of published sizes of the ECV and rates of perspiration. An ECV of 20% of body weight is a conservative choice in patients arriving at the ICU after major surgery [16], while 60% is an extreme estimate [17]. Regarding perspiration, defining the extremes was more difficult, but nearly all sources assume a perspiration ≥400 ml/day for both the skin and for the respiratory tract without fever [14]. Our estimate of 5ml/kg/day probably is thus the lower limit, while 20ml/kg/day is a large estimate. We believe that the true value of both MES and MEC should be somewhere in between the four more extreme scenarios as depicted in Figure 3. MES and MEC were mainly influenced by perspiration and MEC also somewhat by the ECV. This underscores that both the size of the ECV and insensible perspiration are important determinants in the estimated size of MES and MEC. In sex-specific models (Supplementary material: Figure SF1), males showed slightly higher MES and MEC compared with females.

More sodium and chloride disappeared from the balances during the first two days of ICU admission than in the subsequent days (Figure 1). Resuscitation fluids, often high in sodium and chloride content, are frequently administered during surgery and in the early postoperative period. Whereas the recommended limits for dietary sodium intake are 2.3 g/day [18], our patients received an average of 8.3 g (i.e., 360 mmol) sodium per day, with positive sodium balances but stable sodium concentrations. This resulted in a MES of 296 mmol after 4 ICU days. When this MES is expressed in terms of NaCl 0.9% infusion, 1.9L of this fluids sodium went missing in our patients.

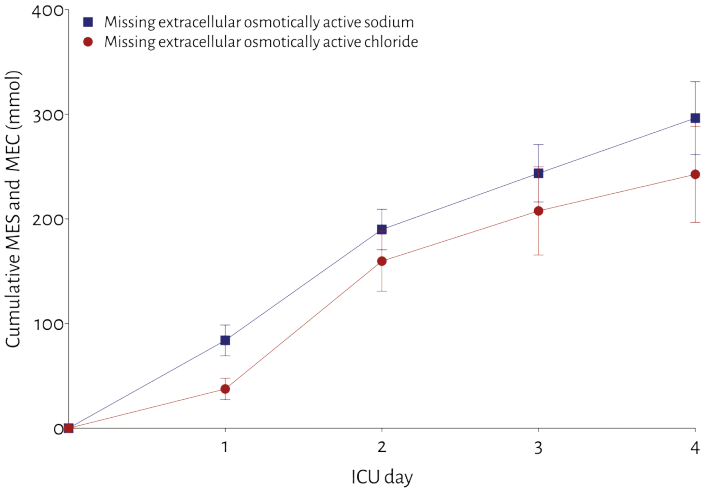


**Figure 1. Time course of estimated cumulative MES and MEC for the first four ICU days.**
Values are depicted as mean ±SE. The first values reflect levels at ICU admission, when storage was assumed defined as zero. The values at the subsequent time points reflect levels at the end (i.e., midnight) of each ICU day. As can be seen under normal and stable circulating electrolyte levels (Table 2), a significant amount of sodium (MES) and chloride (MEC) "disappears" from the balances over the first four ICU days.

Nonosmotic sodium storage has been studied in several non-critically ill patient groups. In healthy individuals it has recently been observed that half of an acute intravenous hypertonic saline load of 201 mmol appears to be briefly stored non-osmotically [19], possibly in interaction with the endothelial glycocalyx. Sodium storage has been reported to increase with advancing age, to be greater in men and patients with hypertension, hyperaldosteronism, end-stage kidney disease and infection [20-22]. Tissue sodium levels are variable and may be altered by dialysis and diuretic treatment [23,24]. However, the precise clinical significance of nonosmotic sodium storage has not been defined yet. The existence of nonosmotic sodium storage has not been examined in critically ill patients. Nonosmotic sodium storage could also be relevant in ICU acquired hypernatremia (IAH) [25] and could explain the relatively long duration of IAH once it develops, although sodium balances were not performed in this study. It is believed that the electrical binding capacity of various tissues for sodium is altered during inflammation [26], which may interact with the development of IAH in critically ill patients. Irrespective of a potential relation between IAH and sodium storage, a strategy in which infusion fluids with lower sodium chloride content are used to reduce IAH is probably desirable [27]. We reported earlier [10] that changes in bulk intravenous fluid constitution paralleled changes in the incidence of ICU-acquired hypernatremia. Recently, it was elegantly shown that maintanance fluid therapy constitutes a higher sodium, chloride and water burden than acute resuscitation fluid administration [28]. With regard to chloride, which also disappeared in our balance calculations, both sodium and chloride storage may affect changes in blood pressure [6,29].

As we can not explain MES and MEC by the conventional two compartment model where sodium is extracellular and potassium intracellular, a specific storage compartment may be the buffer of these sodium and chloride loads. The key alternative to nonosmotic storage is loss of sodium and chloride to the ICV. This effect has been demonstrated by healthy persons who sustained muscular injury [30]. Criticall illness is often accompanied with critical illness myopathy, and loss of sodium and chloride to the ICV might then also be conceivable [30]. As we reported in an earlier study [8], our patients displayed a *negative* potassium balance of 101 mmol, which is another argument for possible intracellular uptake of sodium in exchange for potassium release. Moreover, we also observed a negative electrolyte-free water (EFW) balance in these patients. Together, this suggests that no ICV expansion occurred [8]. Therefore, we assumed that all fluids administered (including EFW) remained in the ECV. However, if part of the EFW would enter the ICV, this would result in lower increases and thus even higher MES and MEC estimates.

The presence of non-osmotic storage could be verified through direct tissue analysis or via specialized MRI [2,3,20]. Sodium changes in the tissues of ICU patients resulting from MES could be imaged via $^{23}$Na MRI. To our knowledge, $^{35}$Cl MRI has not yet been used to study MEC, but it is a promising and intriguing technique to identify the anatomical spaces where salt is stored [32,33]. Importantly, this technique should be able to differentiate between the two main explanations for missing sodium and chloride: nonosmotic storage or intracellular uptake.

Our study has a number of limitations. Due to its retrospective design, we could not control for many variations in standard care. We had to make several assumptions, as for example for the insensible perspiration or the size of the ECV.

However, we believe that the extreme scenarios on perspiration and ECV in our sensitivity analyses covered all realistic scenarios. We did not account for fecal losses, as we could not retrieve this information. Since we observed early post-operative patiens, fecal production was absent or very low and moreover, loss of sodium and chloride through the gut is usually very limited [34]. We did not measure weight changes as this is not routine procedure at our unit. Daily weight measurements could be added in the future to further validate our results.

On the relatively short term, differences in body weight measured in kg as measured in ICU patients will be less accurate than fluid balances measured in ml. Therefore, we only used initial recorded weight to estimate the ECV. Fluid balances in critically ill patients often have a poor correlation with changes in body weight [35,36]. Especially cumulative fluid balance is prone to errors, as measuring errors get cumulated [36], which we accounted for in our error estimates. It must be noted that body weight measurement also has multiple possible errors, which could be the explanation of the lack of association between fluid balance and differences in body weight [36]. However, we believe that due to the short time this study covers and the meticous recalculation of the fluid balance, including gastric retention, drain fluids and insensible perspiration, we have minimized errors as far as realistically possible.

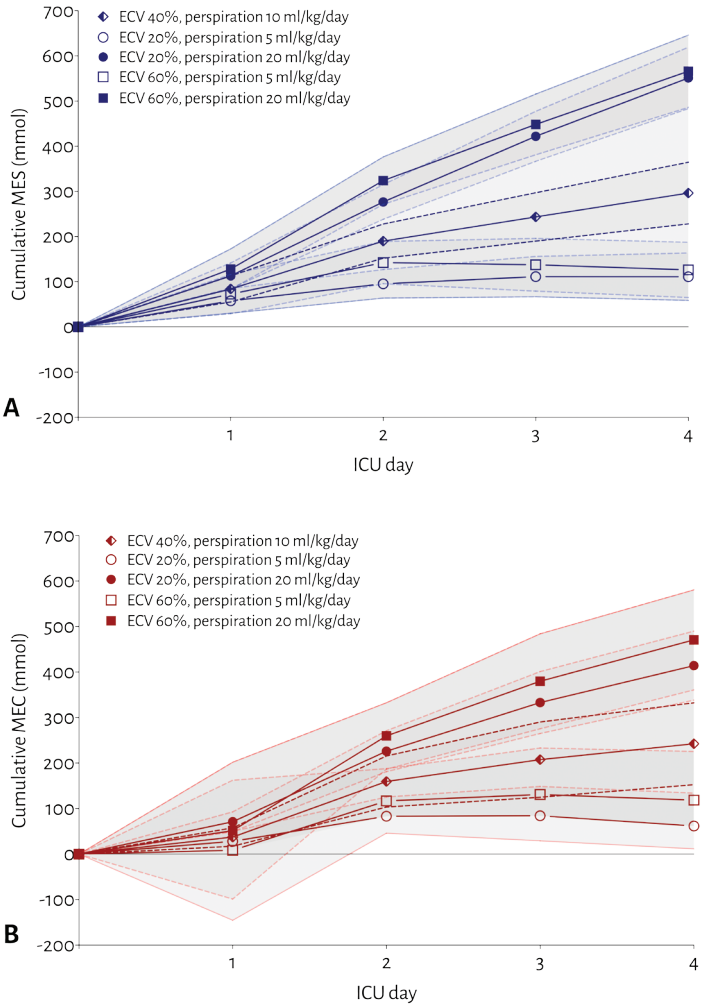


**Figure 2. Scenarios for both estimated cumulative MES and MEC.**

Scenarios for both estimated cumulative MES and MEC. Values are depicted as mean±95% CI. The 95% CI is represented by the dotted lines. The first values reflect levels at ICU admission, when storage was assumed to be zero. In all scenarios, there were considerable MES and MEC after 4 days of ICU admission.

A. With stable sodium levels, MES is mostly influenced by altering the insensible perspiration.

B. MEC showed a similar pattern as MES, but was slightly more affected by the changes in the extracellular compartment than MES.

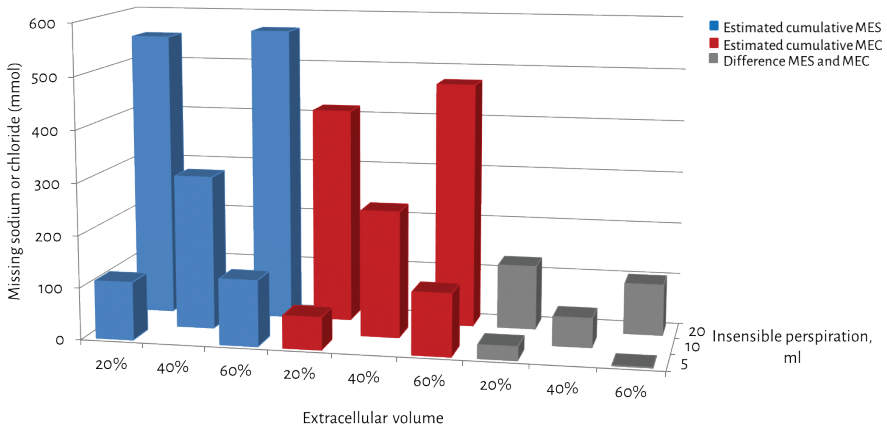


**Figure 3. Estimated cumulative MES and MEC according to different scenarios.**

Values are depicted as means. The calculated MES (blue), MEC (red) and their difference (light gray) on ICU day 4 according to the scenarios with different assumptions on perspiration and the size of the extracellular volume.

Insensible perspiration remains very challenging to measure. As MES and MEC were most influenced by insensible perspiration, the lack of direct measurement of perspiration is a limitation of our study. We tried, however, to maximize the chance to include the true value as much as possible with our five different scenarios. Direct measurement of (in)sensible perspiration would make estimated of MES and MEC more accurate (Figure 3). Unfortunately, we are not aware of reliable tools to measure (in)sensible perspiration.

In this first observational balance study, we selected our patients based on complete balance data, which could have induced selection bias. The Androque-Madias [37] and Nguyen-Kurtz [38] formulas are frequently used when estimating the plasma sodium level after a saline infusion in dysnatremic ICU patients [17,19]. However, we choose not to use these formulas in our study, as they do not account for excretion of sodium or chloride or they use empirically derived constants which were not suitable for using in our model. However, predictions on the size of the ECV from both formulas fall within the four scenarios.

In conclusion, our detailed sodium and chloride balances in ICU patients after cardiothoracic surgery suggest a loss of osmotically active sodium and chloride from the ECV. The estimates depend considerably on the scenarios used. Whether these ions are nonosmotically stored or transferred to the intracellular space needs further study

## ACKNOWLEDGEMENTS

We would like to thank Flip Baardman, Rients de Boer en André Fitze for meticulously recording patient data.

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# ESTIMATION OF SODIUM AND CHLORIDE STORAGE IN CRITICALLY ILL PATIENTS: A BALANCE STUDY

## CHAPTER 8

Supplementary material

# TABLES

All tables are compatible with:
*Hessels L, et al. Postoperative fluid retention after heart surgery is accompanied by a strongly positive sodium balance and a negative potassium balance. Phys Rep. 2016;4:e12807*

**Table S1. Constants and calculations**

| **Calculations** | |
|---|---|
| *Intake of water, sodium, chloride and potassium* | |
| Intake = infusion fluids + given medication + water (oral) | |
| For electrolytes (mmol): | volume * $[electrolyte]_{administered\ fluid}$ (see Table 2,3) |
| *Output of water, sodium, chloride and potassium* | |
| Output = gastric retention + drain production + insensible perspiration + diuresis (24h urines) | |
| For electolytes (mmol): | volume * $[electrolyte]_{administered\ fluid}$ (see Table 2,3) |
| *Balance of water, sodium, chloride and potassium* | |
| Balance = intake – output | |
| Gastric retention: | Volume * $[electrolyte]_{enteral/parenteral\ feeding}$ (see Table 2) |
| Drain fluid loss: | Volume * mean blood [electrolyte] |
| Insensible perspiration: | 10 ml/kg/day<br>+ 2.5ml/kg/day per degree centigrade above 37°C<br>(max body weight in equation: 100 kg)<br>* 0.6 if intubated<br>* 0.5 on admission day |
| Temperature: | Mean body temperature of the day (mean of Temperature at 6h and 18h) |
| **Blood (mmol/L)** | |
| Mean blood sodium: | 132 |
| Mean blood chloride: | 108 |
| **Scenarios** | |
| Default | $ECV_{last}$ = 0.4 x body weight (kg) + fluid balance (L)<br>Insensible perspiration: 10 ml/kg/day |
| A | $ECV_{last}$ = 0.2 x body weight (kg) + fluid balance (L)<br>Insensible perspiration: 5 ml/kg/day |
| B | $ECV_{last}$ = 0.6 x body weight (kg) + fluid balance (L)<br>Insensible perspiration: 5 ml/kg/day |
| C | $ECV_{last}$ = 0.2 x body weight (kg) + fluid balance (L)<br>Insensible perspiration: 20 ml/kg/day |
| D | $ECV_{last}$ = 0.6 x body weight (kg) + fluid balance (L)<br>Insensible perspiration: 20 ml/kg/day |

**Table S2. Electrolyte content of infusion fluids**

| | [$Cl^-$](mmol/L) | [$Na^+$](mmol/L) |
|---|---|---|
| **Resuscitation fluids** | | |
| Voluven® | 154 | 154 |
| Sterofundin® | 127 | 145 |
| Lactated Ringers | 111 | 134 |
| NaCl 5% | 856 | 856 |
| Glucose 5% | 0 | 0 |
| Glucose 50% | 0 | 0 |
| Glucose 2.5%/NaCl 0.45% | 77 | 77 |
| NaCl 0.9% | 154 | 154 |
| **Parenteral/enteral feeding** | | |
| Nutrison protein plus® | 22.57 | 48.26 |
| Nutrison concentrated® | 22.57 | 43.5 |
| Nutrison multifibre® | 35.27 | 43.5 |
| Nutridrink® | 40.67 | 24.54 |
| Peptisorb® | 35.27 | 43.5 |
| TPN | 45 | 35 |
| **Blood products** | | |
| RBC | 80 | 126 |
| FFP | 80 | 172 |
| Thrombocyte concentrate | 70 | 120 |
| Cirrestor blood | 0 | 140 |
| Cell saver blood | 100 | 140 |
| Albumin 20% | 100 | 100 |
| Fibrinogen | 0 | 71 |
| Thrombocyte concentrate | 70 | 120 |

**Table S3. Solutions used to dissolve frequently used medication**

| Type of medication | Dissolved in infusion fluid* |
|---|---|
| Propofol 2% | None |
| Midazolam 100mg/50 ml | NaCl 0.9% |
| Morphine 100mg/50 ml | NaCl 0.9% |
| Insulin 50 IU/50 ml | NaCl 0.9% |
| Noradrenaline 10 mg/50ml | Glucose 5% |
| Adrenaline 10 mg/50 ml | NaCl 0.9% |
| Dobutamine 250mg/50ml | NaCl 0.9% |
| Dopamine 200mg/50 ml | NaCl 0.9% |
| Amiodarone 600mg/50 ml | Glucose 5% |
| Nicardipin 10 mg/50 ml | NaCl 0.9% |
| Milrinone 10 mg/50 ml | NaCl 0.9% |
| Magnesium sulfate | NaCl 0.9% |
| Furosemide 80 mg/50 ml | NaCl 0.9% |
| Nitroglycerin 10 mg/50 ml | NaCl 0.9% |
| Vasopressin 40 U/40 ml | NaCl 0.9% |
| Tacrolimus 2mg/50 ml | NaCl 0.9% |
| Sodium phosphate | NaCl 0.9% |
| Dexmedetomidine | Glucose 5% |
| Clonidine 600 ug/50 ml | NaCl 0.9% |
| Hydrocortisone 200 mg/50 ml | NaCl 0.9% |
| Heparin 20,000 IU/50 ml | NaCl 0.9% |
| Piperacillin/Tazobactam (4/500) | Water ($[Na^+]_{end}$ =196 mmol/L) |
| Fluxocacillin | NaCl 0.9% ($[Na^+]_{end}$ =418 mmol/L) |
| Naloxone | NaCl 0.9% |
| Tranexaminic acid | NaCl 0.9% |
| Labetalol 250 mg/50 ml | None |
| Mycophenolate mofetil | Glucose 5% |
| Ganciclovir | NaCl 0.9% |
| Levosimendan | Glucose 5% |
| Protamine | NaCl 0.9% |
| Phenylephrine | NaCl 0.9% |

*Infusion fluids according to our institutions protocol at the time of the study. Since then, several dissolving fluids have been changed into glucose 5%.

## FIGURES

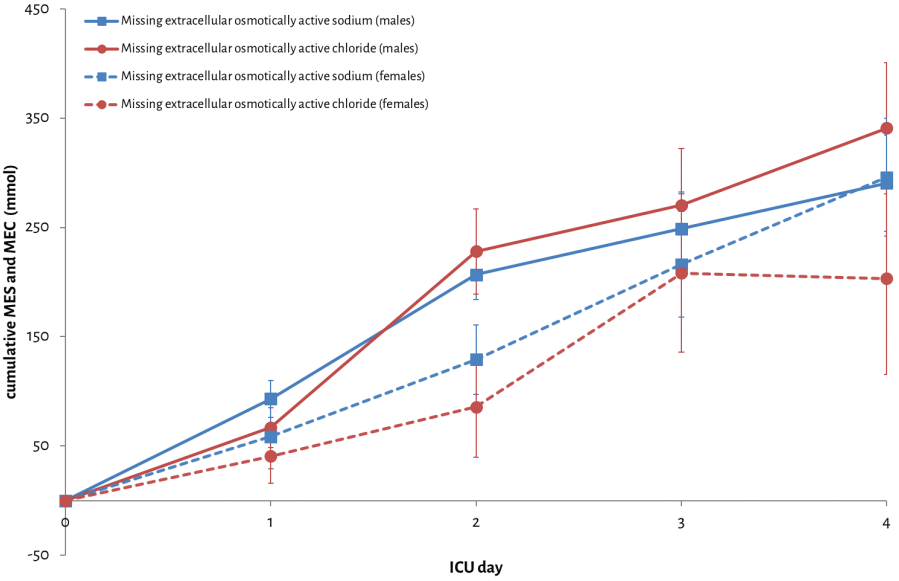
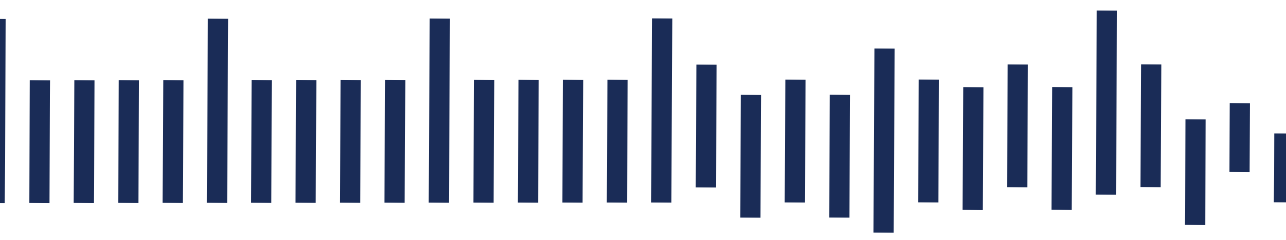



**Figure S1. Time course of estimated cumulative MES and MEC for the first four ICU days in males and females**
Values are depicted as mean±SE. The first values reflect levels at ICU-admission, when storage was assumed defined as zero. The values at the subsequent time points reflect levels at the end (i.e., midnight) of each ICU day. As can be seen under normal and stable circulating electrolyte levels (Table 2), a significant amount of sodium (MES) and chloride (MEC) "disappears" from the balances over the first four ICU days. ECV has been defined as 40% of bodyweight for males and 30% of bodyweight for females. At day 4 the differences between males and females were not significant (MES: $P = 0.95$ , MEC $P = 0.23$).



# CHAPTER 9

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# URINARY CREATININE EXCRETION IS RELATED TO SHORT-TERM AND LONG-TERM MORTALITY IN CRITICALLY ILL PATIENTS

**Intensive Care Medicine 2018;44(10)1699-1708.**

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**Both authors contributed equally*

## ABSTRACT

### PURPOSE

Patients with reduced muscle mass have a worse outcome, but muscle mass is difficult to quantify in the ICU. Urinary creatinine excretion (UCE) reflects muscle mass, but has not been studied in critically ill patients. We evaluated the relation of baseline UCE with short-term and long-term mortality in patients admitted to our ICU.

### METHODS

Patients who stayed ≥24h in the ICU with UCE measured within 3 days of admission were included. We excluded patients who developed acute kidney injury stage 3 during the first week of ICU stay. As muscle mass is considerably higher in men than women, we used sex-stratified UCE quintiles. We assessed the relation of UCE with both in-hospital mortality and long-term mortality.

### RESULTS

From 37,283 patients, 6151 patients with 11,198 UCE measurements were included. Mean UCE was 54% higher in males compared to females. In-hospital mortality was 17%, while at 5-year follow-up, 1299 (25%) patients had died.

After adjustment for age, sex, estimated glomerular filtration rate, body surface area, reason for admission and disease severity, patients in the lowest UCE quintile had an increased in-hospital mortality compared to the patients in the highest UCE quintile (OR 2.41, 95%CI 1.83-3.17). For long-term mortality, the highest mortality risk was also observed for patients in the lowest UCE quintile (HR 2.27, 95% CI 1.84-2.80), independent of confounders.

### CONCLUSIONS

In ICU patients without severe renal dysfunction, low urinary creatinine excretion is associated with short-term and long-term mortality, independent of age, sex, renal function and disease characteristics, underscoring the role of muscle mass as risk factor for mortality and UCE as relevant biomarker.

# INTRODUCTION

Muscle mass is an important determinant of the ability of patients in the intensive care unit (ICU) to overcome their disease. Sarcopenia (i.e., loss of muscle and function) on ICU admission is an independent risk factor for morbidity and mortality in critically ill patients [1-3]. Although several physical and laboratory indicators of muscle mass have been used in various other patient groups [4,5], muscle mass is difficult to quantify in ICU patients.

Creatinine is the stable end product of creatine. Most creatine is present in muscle and is converted at a steady rate to creatinine. Creatinine is released into the circulation and is almost exclusively excreted in the urine [6]. In steady state conditions, urinary excretion will equal creatinine production, irrespective of the serum creatinine concentration. Therefore measurement of urinary creatinine excretion (UCE) in 24-h urine collections is a widely accepted method for muscle mass estimation in stable outpatient populations [5,7-9]. In healthy subjects [10] and in patients with wasting conditions or (chronic) renal failure [4,8], UCE has been associated with long-term mortality.

UCE has not been evaluated in critically ill patients. In our ICU, 24-h urine is routinely and continuously collected to measure UCE. We hypothesized that in critically ill patients baseline UCE as a reflection of muscle mass is related with mortality. We analyzed the relation of UCE with short-term and long-term mortality.

# MATERIALS AND METHODS

## STUDY SETTING, PATIENT SELECTION AND OUTCOME

In this retrospective observational cohort study, we analyzed laboratory measurements of all patients aged 15 years and older who were admitted to our ICU in a university hospital between January 2002 and April 2016. Reason for ICU-admission, age, sex, height, weight and the acute physiology and chronic health evaluation score 4 (APACHE-IV) [11] were recorded. We routinely collect 24h urine samples as part of standard care at our ICU to determine the measured creatinine clearance. From 00:00 to 24:00 all urine in collected in a large disposable container.

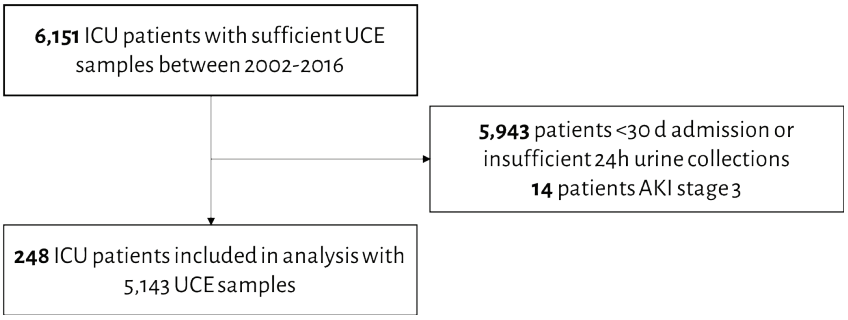


**Figure 1. Flowchart of patients included into the analysis**

Patients who were discharged within 24-h of ICU admission or for whom no 24-h urine samples were available in the first 3 days after admission (i.e., due to measurement errors in the lab or incomplete 24-h collections) were excluded. Only 24-h urine samples collected in the first 3 days after ICU admission were analyzed. UCE was determined by multiplying the urinary creatinine concentration in the 24-h urine with the 24-h urinary volume. We did not used weight-adjusted daily UCE, as we do not routinely weigh our patients. The median UCE was calculated for each patient and used for further analyses. Corresponding daily serum creatinine levels were also available. Acute kidney injury (AKI) was assessed for the first 7 days of ICU admission. Patients with acute kidney injury (AKI) stage 3 (i.e., increase of serum creatinine to >300% from baseline, or ≥ 354 µmol/L (4 mg/dL) or requiring renal replacement therapy [12]) during the first 7 ICU days, were excluded because of their inability to produce urine or unreliability of UCE as RRT interferes with UCE interpretation. Since complete data on urine output were often not available, we only used the serum creatinine based criteria of the KDIGO AKI guideline.
We stratified for sex to account for the considerable difference in creatinine excretion resulting from differences in body weight and composition between men and women [13]. This study was approved by our hospital's medical ethical committee and since it concerned an analysis of anonymized laboratory and clinical data, all collected during standard clinical care, informed consent was not required (METc 2011/132).

## SAMPLES

Urinary and serum creatinine measurements were performed in the hospital's certified central laboratory. Serum creatine kinase activity (CK) measured at ICU day one was also recorded to assess a possible effect of rhabdomyolysis on creatinine. Potential rhabdomyolysis was defined as CK ≥1500 U/l. Cardiothoracic surgery patients were not included in this subgroup. We did not exclude patients with potential rhabdomyolysis. Estimated glomerular filtration (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [14] with serum creatinine, sex, and age as input variables. Body mass index (BMI) was calculated as weight (kg)/height2 (m2). In order to adjust for acute changes in renal clearance of creatinine we also calculated the estimated creatinine production, as described in the Supplementary material. Likewise, in the SMF we compared weight-adjusted UCE, i.e., UCE/kg with UCE in the predictive models in patients with available baseline body weight measurements.

**Table 1. Patient characteristics and outcome parameters**

| | UCE sex-stratified quintiles[a] | | | | | |
|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 | *P* |
| Included patients | 1,228 | 1,237 | 1,208 | 1,240 | 1,238 | |
| Male (%) | 760 (62%) | 770 (62%) | 756 (63%) | 764 (62%) | 764 (62%) | 0.987 |
| Age, years | 67 (56 - 76) | 67 (58 - 76) | 66 (56 - 73) | 60 (48 - 69) | 51 (38 - 61) | <0.001 |
| Urinary creatinine excretion, mmol/24h | 5.3 ±2.0 | 8.4 ±1.7 | 10.6 ±2.2 | 12.9 ±2.8 | 17.2 ±4.5 | <0.001 |
| Men | 6.0 ±1.9 | 9.7 ±0.7 | 12.2 ±0.7 | 15.0 ±0.9 | 20.0 ±3.1 | <0.001 |
| Female | 4.0 ±1.3 | 6.3 ±0.5 | 7.8 ±0.4 | 9.5 ±0.6 | 12.8 ±2.4 | <0.001 |
| Reason for admission (%) | | | | | | <0.001 |
| Medical | 173 (14%) | 129 (10%) | 126 (10%) | 158 (13%) | 153 (12%) | |
| Surgical | | | | | | |
| Trauma | 35 (3%) | 48 (4%) | 58 (5%) | 117 (9%) | 279 (23%) | |
| Abdominal/vascular | 288 (23%) | 297 (24%) | 291 (24%) | 315 (25%) | 289 (23%) | |
| Transplantation | 54 (4%) | 66 (5%) | 54 (4%) | 51 (4%) | 18 (2%) | |
| Neurosurgery | 31 (3%) | 32 (3%) | 41 (3%) | 59 (5%) | 86 (7%) | |
| Cardiothoracic | 243 (20%) | 319 (26%) | 347 (29%) | 286 (23%) | 193 (16%) | |
| Miscellaneous | 408 (33%) | 346 (28%) | 291 (24%) | 254 (21%) | 220 (18%) | |
| ICU LOS, days | 4.8 (2.6-10.1) | 4.9 (2.7-10.1) | 4.1 (2.3-8.7) | 4.3 (2.3-9.6) | 4.5 (2.5-9.8) | 0.004 |
| Hospital LOS, days | 18.1 (9.2-34.7) | 20.2 (12.1-34.2) | 17.4 (11.2-30.0) | 16.9 (10.3-28.2) | 16.8 (10.2-28.7) | <0.001 |
| APACHE-IV[b] | 73 ±27 | 67 ±24 | 64 ±24 | 58 ±24 | 53 ±23 | <0.001 |
| Length, cm[c] | 171 ±10 | 173 ±9 | 174 ±9 | 176 ±9 | 178 ±9 | <0.001 |
| Weight,kg[d] | 73 ±16 | 75 ±14 | 80 ±15 | 83 ±15 | 90 ±18 | <0.001 |
| BMI[c] | 25 ±5 | 25 ±4 | 26 ±4 | 27 ±5 | 28 ±6 | <0.001 |
| BSA, $m^2$[c] | 1.8 ±0.2 | 1.9 ±0.2 | 2.0 ±0.2 | 2.0 ±0.2 | 2.1 ±0.2 | <0.001 |
| Acute kidney injury | 539 (44%) | 414 (34%) | 305 (25%) | 233 (19%) | 218 (18%) | <0.001 |
| Stage 1 | 353 (65%) | 301 (73%) | 229 (75%) | 173 (79%) | 163 (64%) | |
| Stage 2 | 186 (35%) | 113 (27%) | 76 (25%) | 60 (27%) | 55 (25%) | |
| Serum creatinine, umol/L | 86 (56-136) | 76 (58-115) | 73 (58-100) | 70 (58-93) | 69 (58-87) | <0.001 |
| eGFR (mL/min/1.73m2) | 72 (40-102) | 82 (51-100) | 87 (61-101) | 93 (69-107) | 100 (81-114) | <0.001 |

[a]Urinary creatinine excretion quintiles based on separate quintiles intervals for males and females in mmol per day. Q1, ♂≤8.25; ♀ ≤5.55 mmol/d; Q2, ♂ >8.25-10.80; ♀ >5.55-7.10 mmol/d; Q3, ♂ >10.80-13.45; ♀ >7.10-8.55 mmol/d; Q4, ♂ >14.35-16.65; ♀ >8.55-10.50; Q5, ♂ >16.65; ♀ >10.50 mmol/d

[b]Data missing of 1,709 (28%) patients.

[c]Data missing of 1,176 (19%) patients.

[d]Data missing of 1,173 (19%) patients.

## OUTCOME

In-hospital mortality was used as the short-term outcome measure. We performed complete long-term follow-up to record mortality in patients for 5 years after hospital discharge, as recorded in the hospital database and in the municipal mortality registry by January 2018.

## STATISTICAL ANALYSIS

Patient characteristics were calculated according to sex-stratified UCE quintiles. Data were expressed as mean and standard deviation (SD) when normally distributed or median and interquartile range (IQR) when skewed. A Chi-square test for categorical variables and ANOVA for normally distributed continuous variables or a Kruskal-Wallis test for skewed distributed continuous variables was performed to determine variances between patient characteristics across UCE quintiles. Missing data were imputed via multiple imputation (see Supplementary material).

To assess associations of UCE with short-term and long-term mortality respectively, multivariable logistic regression and Cox proportional hazards regression analyses were performed. The proportional hazard assumption was verified by inspection of "log-log" plots and by introducing interactions with survival time. UCE was entered as a categorical variable (quintiles) and as a continuous variable (with OR/HR calculated per 5 mmol/24h UCE decrease). Analyses were first performed in a crude model (model 1: adjusted for sex when UCE as entered as continuous variable). Further analyses cumulatively included adjustment for age (model 2), eGFR (model 3), BMI (model 4) and reason of admission and severity of illness (model 5). For patients discharged alive from the hospital, long-term survival was assessed with Kaplan-Meier survival curves according to the sex-stratified UCE quintiles and evaluated with the log-rank test. Patients who were lost to follow up were censored at that particular time point. Splines were fit by a logistic regression model and a Cox proportional hazards regression model based on restricted cubic splines and adjustments as used in model 5. In secondary analyses, we tested for potential interaction by sex, age, BSA, renal function, disease severity and reason of admission. We also performed separate analyses for patients who developed AKI and for patients that did not develop AKI. Additional subgroup analyses were performed when effect modification was observed or when differences in UCE were expected in patient subgroups. In sensitivity analyses, we investigated for potential bias introduced by imputation, by restricting the dataset to complete cases. As additional sensitivity analysis, we assessed the potential confounding effect of rhabdomyolysis on UCE. Serum CK was log transformed to adjust for its strongly skewed distribution. The secondary and sensitivity analyses as listed in the results and SMF were adjusted for potential confounders that were included in model 5. *P* values < 0.05 were considered significant. Data were analyzed with SPSS 23.0 (IBM Inc.2016, New York, USA) and R version 3.4.2 (R foundation for Statistical Computer, Vienna, Austria).

# RESULTS

## PATIENT CHARACTERISTICS AND OUTCOME

Of a total of 37,283 patients, 6,151 patients were included. We excluded 28,493 patients because of ICU admission with a duration shorter than 24h or incomplete 24-h urine collection. Another 2,572 patients were excluded because of AKI stage 3 within 7 days of ICU admission and finally 67 patients were excluded because of missing serum creatinine levels. In the remaining 6,151 patients, a total of 11,198 24-h urine creatinine measurements (i.e., 1.8 measurement per patient) were determined during the first 3 ICU days (Figure 1). The baseline clinical characteristics of the included patients are summarized in Table 1. Median age of the included patients was 62 (50-72) years and 62% were male. Median UCE (IQR) was 54% higher in men than women, i.e., 12.2 (9.0 – 15.7) vs. 7.9 (6.0 – 10.1) mmol/24h ($P < 0.001$). The mean UCE was similar on ICU days 1 and 3 (10.8±5.2 vs. 11.0±5.1 mmol/24h, $P = 0.34$). Median urinary volume was 1.5 L (1.01-2.2). Reason for admission differed between the quintiles of UCE, with the highest number of trauma patients in the highest UCE quintile.

**Table 2. Logistic regression of in-hospital mortality**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | (n=6,151) | | Q1 | Q2 | Q3 | Q4 | Q5 |
| | | | (n=1,228) | (n=1,237) | (n=1,208) | (n=1,240) | (n=1,238) |
| | OR (95% CI) | *P* | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | Reference |
| Model 1[b] | 1.81 (1.66-1.97) | <0.001 | 4.34 (3.46-5.45) | 2.24 (1.77-2.85) | 1.58 (1.23-2.03) | 1.32 (1.02-1.71) | 1.00 |
| Model 2[c] | 1.67 (1.52-1.83) | <0.001 | 3.32 (2.61-4.20) | 1.69 (1.32-2.17) | 1.22 (0.94-1.59) | 1.14 (0.88-1.48) | 1.00 |
| Model 3[d] | 1.65 (1.51-1.81) | <0.001 | 3.21 (2.52-4.08) | 1.68 (1.30-2.16) | 1.24 (0.95-1.61) | 1.15 (0.88-1.50) | 1.00 |
| Model 4[e] | 1.70 (1.54-1.88) | <0.001 | 3.47 (2.69-4.49) | 1.80 (1.38-2.33) | 1.30 (0.99-1.70) | 1.19 (0.91-1.55) | 1.00 |
| Model 5[f] | 1.49 (1.34-1.65) | <0.001 | 2.56 (1.96-3.34) | 1.45 (1.11-1.91) | 1.09 (0.83-1.43) | 1.08 (0.82-1.41) | 1.00 |

Multivariable logistic regression to assess the association of UCE with in-hospital mortality.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs non-trauma).

The median ICU length of stay was 4.6 (2.5 – 9.7) days, with a total hospital stay of 17.9 (10.8 – 30.7) days (Table 1). The median serum creatinine was 73 (57-104) µmol/L and 1709 patients (28%) developed AKI stage 1 or stage 2 in the first week of ICU stay. Serum creatinine decreased in the first 3 ICU days (day 1: 79 [62-104], day 3: 73 [57-106] µmol/L, $P < 0.001$). Serum creatinine and incidence of AKI were inversely associated with UCE quintiles. Median eGFR was 92 (60-122) ml/min and was positively associated with UCE quintiles. Median follow-up time was 3.7 (2.1-7.6) years with a maximum of 16.1 years. A completeness of follow-up of 85% was achieved (Supplementary material).

## UCE AND SHORT-TERM MORTALITY

Overall in-hospital mortality was 17%. In-hospital mortality decreased for the sex-specific quintiles of UCE, from 31% in the first quintile to 9% in the fifth quintile (P < 0.001, Figure 2A). In multivariable logistic regression analyses with sex-specific quintiles of UCE, there was a 2.4 times increased risk of in-hospital mortality in the lowest sex-specific UCE quintile compared to highest quintile (OR: 2.56, 95%CI 1.96-3.34, $P < 0.001$), independent of potential confounders (Table 2, model 5). In multivariable logistic regression analyses, with adjustment for sex, UCE expressed as a continuous variable was inversely associated with in-hospital mortality (for each 5 mmol/24h decrease of UCE: OR 1.81, 95% CI 1.66-1.97, $P < 0.001$; Table 2). This association remained significant (OR 1.49, 95%CI 1.34-1.65, $P < 0.001$), independent of potential confounders (Table 2, model 5).

Because of the known sex difference in UCE, multivariable adjusted restricted cubic splines for the association of UCE with in-hospital mortality are shown separately for men and women in Figure 3.

## UCE AND LONG-TERM MORTALITY

For the 5,111 patients who were discharged alive from the hospital, long-term mortality was assessed. Overall 5-year mortality was 29%. In univariate analysis, UCE showed a strong relation with long-term survival as illustrated by the Kaplan-Meier curves (log-rank test $P < 0.001$, Figure 2B). In Cox-regression with UCE expressed in quintiles, patients in the lowest UCE quintile had a 4 times higher risk for long-term mortality compared to those in the highest UCE quintile (HR 4.03, 95%CI 3.35-4.84, $P < 0.001$, Table 3). After adjustment for potential confounders, this association remained independent (HR 2.32, 95% CI 1.89-2.85, $P < 0.001$, Table 3, model 5).

In Cox regression analysis with UCE expressed as a continuous variable, UCE was also associated with long-term mortality (HR 1.76, 95%CI 1.66-1.88 for each 5 mmol/24h decrease of UCE, $P < 0.001$, Table 3). This association remained independent after adjustment for confounders with an HR of 1.49 (95%CI 1.38-1.62, $P < 0.001$, Table 3, model 5).
A multivariable adjusted restricted cubic spline for the association between UCE and mortality over 5 years for both men and women is shown in Figure 4.

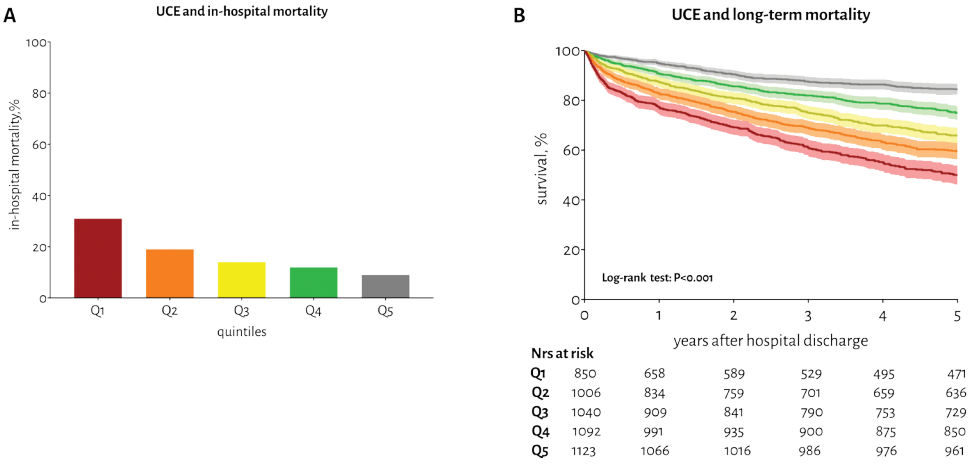


**Figure 2. Short-term and long-term mortality as expressed in UCE quintiles.**

A. In-hospital mortality is depicted for the UCE quintiles in percentages. The first quintile represents the lowest UCE, the fifth quintile represents the highest quintile. Corresponding quintile cut-off values are shown in Table 1. In-hospital mortality increased when baseline UCE decreased (Chi-square test: $P < 0.001$).

B. Kaplan-Meier curves for 5 year survival (with 95% CI) after hospital discharge. The colors of the quintiles correspond to colors as depicted in Figure 2A. The highest UCE quintile had the best 5-year survival, which declined with declining baseline UCE (log-rank test: $P < 0.001$).

## SUBGROUP, SENSITIVITY AND ADDITIONAL ANALYSES

Additional subgroup and sensitivity analyses concerning the role of AKI, BMI and rhabdomyolysis amongst others, are presented and shown in the Supplementary material (Tables ST1-ST10, Figures SF1-SF11). We found similar associations between UCE and short-term and long-term mortality in both the subgroup and sensitivity analyses. Only the association between UCE and short-term mortality was not observed in trauma patients (OR 1.10, 95%CI 0.71-1.71, $P = 0.66$).

## DISCUSSION

This large prospective study shows that urinary creatinine excretion (UCE) early after ICU admission as a measure of muscle mass is strongly associated with both short-term and long-term mortality, independent of important covariates and confounders, including disease severity, age and renal function.

We consistently observed an inverse association between UCE and both short-term and long-term mortality, even in patients with chronic kidney disease or AKI (Supplementary material: Tables ST1-ST10, Figure SF4). Only for short-term outcome in trauma patients, no independent association with UCE was observed. However, a stronger association of UCE with long-term mortality was seen in the trauma patients when compared to the total patient group (Supplementary materia: Table ST4). As hospital mortality of severe trauma patients is mainly determined by age, severity of coma after trauma (and thus brain injury), base excess and coagulation disturbances [15], UCE is likely to be only a minor determinant of the short-term prognosis of trauma patients.

The relation of UCE with mortality has already been established in several other patient groups. A higher mortality in patients with low (baseline) UCE is present in renal transplant patients [16] and patients with stroke [17], coronary artery disease [8], heart failure [18] and chronic kidney disease [19]. Moreover, a similar association is observed in the general population [10]. We are the first to examine the relationship of UCE with mortality in a large heterogenic critically ill patient group.

**Table 3. Cox proportional hazard regression analyses for 5-year mortality**

| | **UCE[a]** | | **UCE sex-stratified quintiles** | | | | |
|---|---|---|---|---|---|---|---|
| | (n=5,111) | | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** |
| | | | (n=850) | (n=1,006) | (n=1,040) | (n=1,092) | (n=1,123) |
| | HR (95% CI) | *P* | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | Reference |
| Model 1[b] | 1.76 (1.66-1.88) | <0.001 | 4.03 (3.35-4.84) | 3.02 (2.51-3.64) | 2.36 (1.95-2.86) | 1.65 (1.35-2.01) | 1.00 |
| Model 2[c] | 1.56 (1.45-1.68) | <0.001 | 2.58 (2.13-3.13) | 1.88 (1.55-2.28) | 1.53 (1.26-1.87) | 1.25 (1.02-1.53) | 1.00 |
| Model 3[d] | 1.56 (1.45-1.67) | <0.001 | 2.59 (2.14-3.14) | 1.87 (1.54-2.27) | 1.52 (1.25-1.85) | 1.24 (1.01-1.52) | 1.00 |
| Model 4[e] | 1.56 (1.45-1.68) | <0.001 | 2.59 (2.12-3.17) | 1.87 (1.53-2.29) | 1.52 (1.24-1.85) | 1.24 (1.01-1.51) | 1.00 |
| Model 5[f] | 1.49 (1.38-1.62) | <0.001 | 2.32 (1.89-2.85) | 1.71 (1.39-2.09) | 1.39 (1.13-1.70) | 1.17 (0.95-1.43) | 1.00 |

Cox proportional hazard regression analysis to assess the association of UCE with 5-year survival.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs non-trauma).

In several ICU subgroups, a J-shaped association between BMI and mortality was shown [20]. Other studies also show a beneficial effect of a moderately elevated BMI in several patient groups, including the critically ill [21-26]. It is very plausible that the increased mortality of patients with a low BMI results from the adverse effects of sarcopenia, as we found the highest mortality risk in patients in the lowest UCE quintile after adjustment for BSA (Tables 2-3).
In patients without AKI, a decreased serum creatinine also is a reflection of muscle wasting [27] and two large studies showed that low baseline serum creatinine is an independent risk factor for mortality [27,28]. Changes in serum creatinine, i.e., in AKI patients, seem only to be associated with short term mortality [29]. Prognostic ICU-models often incorporate serum creatinine as a measure of renal function [11,30]. Although the APACHE-IV score also considers a lowered serum creatinine level (<53 $\mu mol \cdot L^{-1}$ or <0.6 $mg \cdot dL^{-1}$) a mortality risk [11], no prognostic ICU-scoring system utilizes UCE as an outcome predictor. Both serum creatinine and UCE are influenced by renal insufficiency, but in steady state conditions, urinary excretion will equal creatinine production, irrespective of the serum creatinine concentration. UCE will, therefore, better reflect muscle mass than serum creatinine, especially in patients with renal insufficiency. UCE determined early after ICU admission might, therefore, improve prognostic ICU models and could be a significant contribution to the evolution of prognostic scores.

In our study we focused on UCE within 3 days of ICU admission and we did not focus on subsequent changes during ICU admission. In a recent study a decrease in UCE was seen after 7 and 14 days of ICU treatment, reflecting the gradual loss of muscle during ICU stay [31]. It seems plausible that a progressive decrease in UCE would further predict poor outcome, but this has to be assessed in future studies.

Although UCE presents a non-invasive and inexpensive method in ICU-patients, other methods of muscle mass estimation have been well researched in several patient populations, most are poorly suited for ICU patients [32-37]. In the critically ill patient, anthropometric measurements such as body weight, BMI, waist circumference or mid-arm or mid-thigh muscle area are often complicated by the presence of dehydration, ascites or edema. More advanced techniques such as computed tomography, magnetic resonance imaging or dual-energy X-ray absorptiometry are both expensive and impractical for routine use in the ICU [5]. Bioelectrical impedance analysis is a simple and non-invasive method that is widely used to obtain estimates of body composition [38], but its accuracy in detecting loss of muscle mass in ICU patients is questionable because its measurement requires fluid homeostasis [39]. Repeated ultrasonography for the detection of muscle wasting shows promising results in a few relatively small studies [33-35] but muscle dimensions are also influenced by generalized edema. In this regard, it would be interesting to compare UCE with both bioelectrical impedance and ultrasonography in a larger study population, while taking the fluid balance into account.

Some limitations of our study are due to its post-hoc design and the long period it covers. An important potential limitation of UCE are the rapid changes in glomerular filtration rate as are common in the critically ill [40,41].

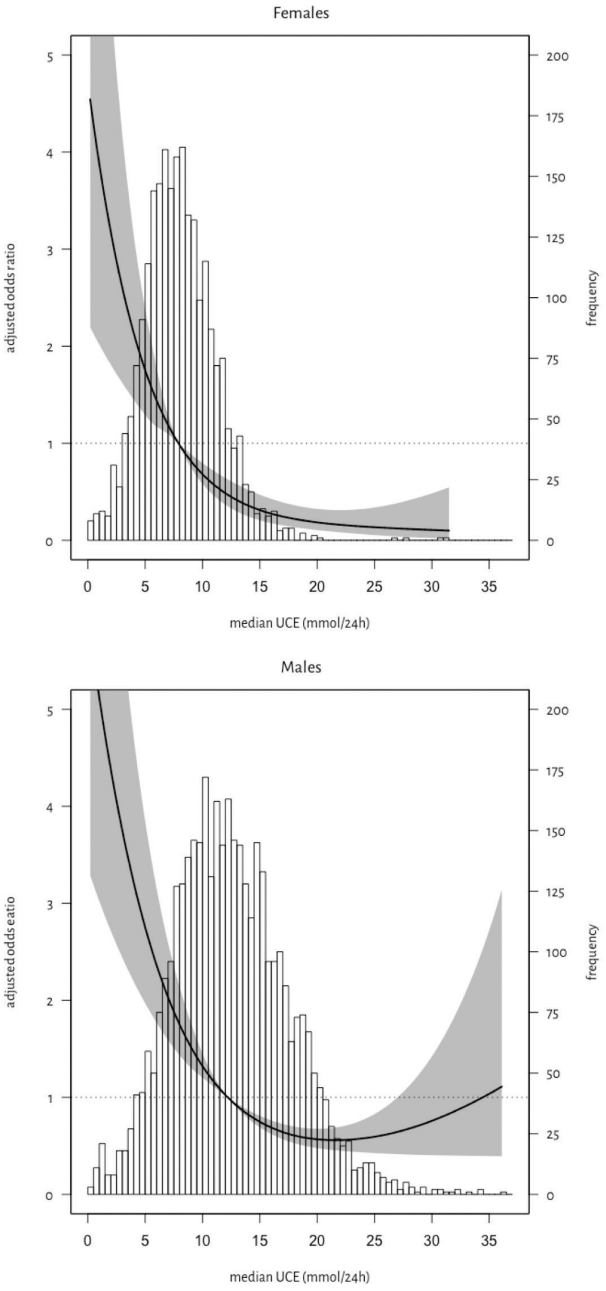


**Figure 3. Association between UCE and in-hospital mortality for both men and women.**
Data were fit by a multivariable logistic regression model based on restricted cubic splines. UCE was entered as continuous variable. Data were adjusted for sex, age, eGFR, BMI, severity of illness and reason of admission (model 5). Here, the median UCE was defined as the reference standard. The gray area represents the 95%CI. The curves in particular underscore the inverse relation of UCE with mortality for low and near median UCE values. Note the widely diverging 95% CI at the extremes resulting from the low patient numbers and the cubic fit.

UCE may decrease in patients with acute kidney injury, who have a higher risk of dying [30]. In some cases, UCE may increase because of augmented renal clearance as has been reported in some younger trauma and sepsis patients [40]. Also the glomerular filtration may be altered by commonly administered drugs, such as vasopressors and diuretics [42,43]. The differences in mortality could thus possibly be attributed to other factors such as renal function or hypercatabolism instead of muscle mass. We were unfortunately not able to address this as we did not perform true GFR measurements or other muscle mass measurements.

The relevance of decreased or increased glomerular filtration or creatinine clearance with respect to UCE could best be addressed by determining this parameter as well. We did adjust for eGFR as potential confounder, however, in case of AKI it may take time before serum creatinine rises, limiting the value of this adjustment. However, mean UCE did not significantly differ between day 1 and 3, and we excluded patients with severe AKI (stage 3). Furthermore, separate analyses performed for both patients without and with AKI stage 1 or 2 (Supplementary material: Table ST3a, ST3b, Figure SF4) led to similar findings. Finally, we excluded patients with AKI stage 3, also because UCE cannot be determined in anuric patients. This is an obvious limitation of using this marker as a prognostic score. Estimation of muscle mass by measurement of UCE also requires complete 24-h urine collection by ICU nurses. Since ICU patients typically have indwelling urine catheters, this was an advantage in our population. In non-ICU patients who often have to collect the 24-h urine themselves, it is therefore considered a less reliable method [4]. Creatinine levels in patients who are on an oral diet may also be increased by meat intake. In our study, this potential confounding factor was of no influence since all patients were on enteral or parenteral feeding containing no dietary meat. Our population consists of predominantly surgical rather than medical ICU patients. However, we saw similar findings in the population of non-surgical ICU patients (Supplementary material) and UCE was found to be a strong predictor of mortality in non-ICU medical patients as well [10, 17-19]. Recently, the sarcopenia index has been proposed as a measure for muscle mass [36,37]. Although promising, we were unable to use this index as it requires cystatine C. Due to the retrospective nature of our study we were not able to compare UCE with other different methods that estimate muscle mass, i.e., the paraspinal muscle surface area at lumbal vertebral levels measured on CT [5,37]. However, future studies could assess the relationship between UCE and other muscle mass measures

In conclusion, low urinary creatinine excretion early after ICU admission is a strong independent predictor of both short-term and long-term mortality after adjustment for BMI, renal function and severity of disease, underscoring a role of muscle mass as risk factor for mortality. UCE thus constitutes a simple, readily available and relevant prognostic biomarker for critically ill patients.

## ACKNOWLEDGEMENTS

We thank Wim Dieperink, PhD, of the Department of Critical Care, University Medical Center Groningen, for administrative support. We also thank Leendert H. Oterdoom, MD PhD, of the Department of Gastroenterology and Hepatology, VU University Medical Center, for reviewing and commenting on earlier drafts of the manuscript.

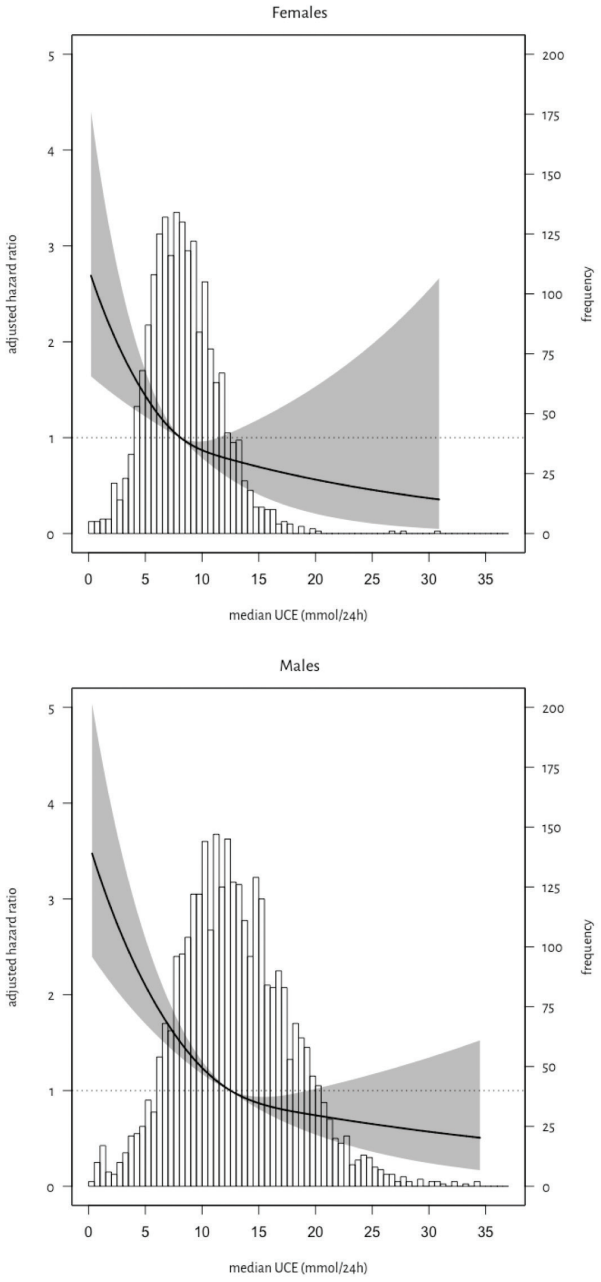


**Figure 4. Association between UCE and 5-year survival for both men and woman discharged alive.**
Data were fit by a Cox proportional hazard regression model based on restricted cubic splines. UCE was entered as continuous variable. Data were adjusted for sex, age, eGFR, BMI, severity of illness and reason of admission (model 5). The gray area represents the 95% CI.

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URINARY CREATININE EXCRETION IS RELATED TO SHORT-TERM AND LONG-TERM MORTALITY IN CRITICALLY ILL PATIENTS

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# CHAPTER 9

Supplementary material

## SUPPLEMENTARY METHODS

### IMPUTATION

For the APACHE-IV score, we set a minimum score of 4 and a maximum score of 171. Minimum and maximum length was defined as 102 cm and 205 cm respectively. For weight, a minimum weight was set at 29 kg and a maximum at 240 kg. The defined range of the imputed variables was based on the ranges of the original data.

### BODY SURFACE AREA

Body surface area (BSA) was calculated as (weight$^{0.425}$ x height$^{0.725}$) x 0.007184.

### ESTIMATED CREATININE PRODUCTION

If UCE is assumed to reflect creatinine production, the UCE does not take into account changes in circulating creatinine due to changes in renal creatinine clearance.

Creatinine generation or the estimated creatinine production was defined as UCE plus the creatinine appearance (or disappearance) in the water compartment of the body, since creatinine is known to distribute over this compartment:

estimated creatinine production =
UCE + (serum creatinine at ICU day N2 - serum creatinine at ICU day N1) x $V_d$

The distribution volume $V_d$ was defined as 0.60 x body weight.

### PREDICTED URINARY CREATININE EXCRETION

We also determined the predicted UCE adjusted for age, weight and gender according to the formula of Bjornsson, *et al*. [1].

males: predicted UCE = (27 - 0.173 x age) x weight
females: predicted UCE= (25 - 0.175 x age) x weight

With this formula, we assessed the association of the difference between the observed UCE and predicted UCE with the in-hospital mortality.

### ROC CURVES

We compared both the predictive of short-term of several parameters by measuring the area under the receiver operating characteristic curve (AUC-ROC) with mortality as outcome parameter.

### FOLLOW UP

We retrieved data on mortality from our hospital database and municipal mortality registry until January 2018. Patients were followed until they either died or when they were lost to follow up, according to the method for actuarial survival analysis. When patients were included in 2016 and alive in 2018, they were censored as they were not followed up after 2 years. We calculated the completeness of follow up according to the formula of Clark, et al. [2] which showed that 85% of the potential follow-up time was covered. Only 2% of the patients were partially lost to follow-up.

## SUPPLEMENTARY RESULTS

### SUBGROUP ANALYSES

In secondary analyses, we found no effect modification on the association of UCE with short-term and long-term mortality (Figure S1). However, we performed secondary analyses on age, renal function, body mass index and reason of admission (i.e., trauma vs. non-trauma), based on expected differences in UCE in these subgroups, since younger and male patients are over-represented in the trauma group (Table 1).

The univariate associations between UCE and short- and long-term mortality are depicted in Figure S2-S5.

#### BMI

First, we compared patients with a BMI ≤30 kg/m2 (n=4,121) and BMI >30 kg/m$^2$ (n=854). UCE was associated with a similar higher in-hospital mortality risk in the lower BMI subgroup (OR 1.56, 95%CI 1.33-1.75, $P < 0.001$) compared to the higher BMI subgroup (OR 1.46, 95%CI 1.10-1.94, $P < 0.001$, model 4, Table S1A). The multivariate association of UCE with long-term mortality was similar for both subgroups (HR 1.58, 95%CI 1.42-1.75, $P < 0.001$ vs. HR 1.39, 95%CI 1.14-1.70, $P = 0.001$, model 4, Table S1B).

#### AGE

We then compared patients below median age (i.e., ≤62 years, n=3,089) with patients above median age (i.e., >62 years, n=3,062). The association between UCE and in-hospital mortality was similar for both groups and showed an inverse, independent association (OR 1.33, 95%CI 1.16-1.53 vs. OR 1.63, 95%CI 1.40-1.91, both $P < 0.001$, model 5, Table S2A). In both younger and older patients, we observed a similar, independent association with UCE and long-term mortality (HR 1.49, 95% CI 1.33-1.68 vs. HR 1.50, 95%CI 1.34-1.67, both $P < 0.001$, model 5, Table S2B).

#### AKI

Subsequently, we compared patients without AKI (AKI 0; n=4,442) with patients with AKI (AKI 1 or AKI 2; n=1,709). Both groups showed similar independent associations between UCE and in-hospital mortality after adjustment for potential confounders (OR 1.48, 95%CI 1.29-1.69, $P < 0.001$ vs OR 1.36, 95%CI 1.15-1.60, $P < 0.001$, model 5, Table S3A). When long-term mortality was assessed in a Cox-regression analysis, the association with UCE was also similar for patients without AKI and patients with AKI (HR 1.55, 95%CI 1.41-1.69 $P < 0.001$ vs. HR 1.52, 95%CI 1.29-1.78, $P < 0.001$, model 5, Table S3B) after adjustment for potential confounders.

#### TRAUMA

Further, we restricted the analyses to trauma patients (n=537). A similar univariate inverse association between UCE and in-hospital mortality was observed (OR 1.92, 95%CI 1.40-2.65, $P < 0.001$, Table S4A). However, after adjustment for confounders, there was no significant association between UCE and in-hospital mortality in trauma patients (OR 1.10, 95%CI 0.71-1.71, $P = 0.685$). In Cox regression analysis, we observed a high mortality risk of 3.33 with every 5 mmol/24h decrease in UCE (HR 3.33, 95%CI 2.38-4.67, $P < 0.001$, Table S4B), even after adjustment of potential confounders (OR 2.21, 95%CI 1.46-3.37, $P < 0.001$).

## CANCER

We also conducted a subgroup analysis of patients with a malignancy related admission. Of 3957 patient (in the period of 01-01-2009 thru 31-03-2016), 354 (9%) malignancy was recorded. The median UCE was 10.6 (7.8 -13.4) mmol/24h in this subgroup. In patients with a known malignancy, a stronger association between UCE and mortality was observed (OR 4.31, 95%CI 2.22 – 8.33, $P < 0.001$), also after adjustment of potential confounders (OR 3.75, 95%CI 1.91 – 7.35, $P < 0.001$). However, for long-term mortality, no association between mortality and UCE was observed (HR1.22, 95% CI 0.99 – 1.50, $P = 0.06$), also not after adjustment of potential confounders (HR 1.20, 95% CI 0.95 - 1.52, $P = 0.11$). It should be noted that – not surprisingly - the cancer patients had a far worse long-term prognosis than other patients.

## NON-SURGICAL

Lastly, we conducted a subgroup analysis of non-surgical (medical) patients (n=1772, 29%). In medical patients a similar association between UCE and short-term mortality was observed (OR 1.10, 95%CI 1.18 – 1.67, $P < 0.001$, model 5). Also for long-term mortality, a similar association was seen (HR 1.51, 95%CI 1.31 – 1.74, $P < 0.001$, model 5).

## SENSITIVITY ANALYSES

As sensitivity analyses, we repeated the analyses in cases with only complete data (70%; n=4,336), without imputation of missing data. Results of these analyses did not essentially differ from those with imputation of missing data. There was an unchanged independent association of UCE with in-hospital mortality (OR 1.56, 95%CI 1.38-1.77, $P < 0.001$; Table S5A, model 5). The association between UCE and long-term survival did not markedly change (HR 1.53, 95%CI 1.39-1.68, $P < 0.001$, Table S5B, model 5).

Analyses were also conducted with correction for body surface area (BSA) instead of BMI. The results of these analyses were similar to those with adjustment for BMI (Table S6).

We also examined the potential impact of rhabdomyolysis on UCE in 367 (6%) patients with a CK ≥1500 U/I. CK was available for 4449 (72%) patients. Linear regression showed only a minor correlation of UCE with CK ($R^2$=0.06). When we corrected UCE for CK≥1500 in trauma patients, we observed similar associations of UCE with both short-term and long-term mortality (OR 1.11, 95%CI 0.71-1.71 $P = 0.650$, HR 2.22 95%CI 1.46-3.37, $P < 0.001$, model 5) compared to the association in trauma patients without adjustment for CK (Table S4).

Although trauma patients with a CK≥1500 had overall higher UCE levels, non-surviving trauma patients had a significantly lower UCE compared to surviving trauma patients regardless of possible rhabdomyolysis (Table S7).

In particular when serum creatinine is not constant, eGFR is not always the most reliable method to calculate glomerular filtration. Measured creatinine clearance (mCC) is then more reliable. We repeated our analyses with mCC as adjustment for renal function instead of eGFR. Both the association with short-term and long-term mortality did not markedly change (OR 1.35, 95%CI 1.18-1.55, $P < 0.001$; HR 1.80, 95%CI 11.62-2.00, $P < 0.001$; Table S8).

We also conducted sensitivity analyses in which we compared patient with serum creatinine changes over 27 umol/L with patients without serum creatinine changes (Table S9). Results of these analyses did not substantially differ from each other.

Lastly, we conducted sensitivity analyses in which we analysed UCE per kilogram. For this analysis, we only analysed patients with known baseline weight. We observed a similar association for short-term a long-term mortality when we compared UCE/kg with UCE (Table S10).

We assessed the predictive value for mortality by estimated creatinine production, the difference between the observed UCE and estimated creatinine production, BMI, mCC and serum creatinine compared to UCE by determining the AUC-ROC.

UCE had an AUC-ROC of 0.637 (95% CI (0.618- 0.656, $P < 0.001$) for short-term mortality.
The median estimated creatinine production was 10.2 (7.3-13.8) mmol/24h. The AUC-ROC was 0.641 (95%CI 0.620 – 0.663, $P < 0.001$) for short-term mortality. The median predicted UCE adjusted for age, gender and weight was 12.3 (10.1-14.9) mmol/24h. The AUC-ROC for the predicted UCE was 0.577 (95%CI 0.556-0.599) for short-term mortality. The median difference between the predicted UCE and UCE was 1.7 (-0.5 – 3.9) mmol/l24h. The AUC-ROC was 0.396 (95%CI 0.374-0.418, $P < 0.001$) for short-term mortality.

The AUC-ROC for BMI was 0.511 (95%CI 0.488-0.533, $P = 0.338$) for short-term mortality.
mCC had a similar AUC-ROC compared to the estimated creatinine production and UCE, namely of 0.659 (95%CI 0.640-0.677, $P < 0.001$) for short-term mortality.

Serum creatinine had a smaller AUC-ROC for short-term mortality (0.401 [95%CI 0.391-0.420, $P < 0.001$]) .

The univariate associations between BMI, mCC, eGFR and serum creatinine and long-term mortality are depicted in Figure S6-S9. The correlation between UCE and estimated creatinine production is depicted in Figure S10 and S11. Serum creatinine for the first 3 ICU days in patients with and without AKI is depicted in Figure S12.

# TABLES

**Table ST1A. Logistic regression analyses of in-hospital mortality in BMI subgroups**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | | | Q1 | Q2 | Q3 | Q4 | Q5 |
| | OR (95% CI) | *P* | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | Reference |
| ≤30kg/m² | (n=4121) | | (n=877) | (n=888) | (n=833) | (n=817) | (n=706) |
| Model 1[b] | 1.92 (1.70-2.17) | <0.001 | 4.18 (3.03-5.77) | 1.94 (1.38-2.73) | 1.25 (0.87-1.79) | 1.26 (0.88-1.82) | 1.00 |
| Model 2[c] | 1.83 (1.60-2.08) | <0.001 | 3.49 (2.49-4.89) | 1.60 (1.12-2.29) | 1.07 (0.73-1.55) | 1.16 (0.80-1.68) | 1.00 |
| Model 3[d] | 1.80 (1.58-2.06) | <0.001 | 3.35 (2.38-4.72) | 1.58 (1.10-2.27) | 1.06 (0.73-1.55) | 1.18 (0.82-1.71) | 1.00 |
| Model 4[e] | 1.56 (1.33-1.75) | <0.001 | 2.30 (1.60-3.29) | 1.21 (0.83-1.77) | 0.84 (0.57-1.25) | 1.06 (0.72-1.56) | 1.00 |
| >30 kg/m² | (n=854) | | (n=114) | (n=106) | (n=159) | (n=206) | (n=269) |
| Model 1[b] | 1.98 (1.55-2.53) | <0.001 | 5.03 (2.73-9.27) | 3.70 (1.95-7.04) | 2.40 (1.28-4.51) | 1.50 (0.80-2.81) | 1.00 |
| Model 2[c] | 1.87 (1.45-2.42) | <0.001 | 4.12 (2.19-7.76) | .87 (1.47-5.63) | 1.85 (0.96-3.59) | 1.23 (0.65-2.37) | 1.00 |
| Model 3[d] | 1.82 (1.38-2.36) | <0.001 | 3.53 (1.84-6.77) | 2.45 (1.24-4.84) | 1.77 (0.91-3.44) | 1.16 (0.61-2.23) | 1.00 |
| Model 4[e] | 1.46 (1.10-1.94) | <0.001 | 2.25 (1.13-4.56) | 1.98 (0.97-4.03) | 1.40 (0.71-2.78) | 1.06 (0.54-2.07) | 1.00 |

Multivariable logistic regression to assess the association of UCE with in-hospital mortality. This analysis was only performed in patients with known baseline BMI (missing patients: n=1176).

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs. non-trauma).

**Table ST1B. Cox proportional hazard regression analyses for 5-year mortality in BMI subgroups.**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | | | Q1 | Q2 | Q3 | Q4 | Q5 |
| | HR (95% CI) | *P* | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | Reference |
| ≤30 kg/m² | (n=3,475) | | (n=619) | (n=748) | (n=739) | (n=724) | (n=645) |
| Model 1[b] | 1.90 (1.73-2.08) | <0.001 | 4.63 (3.50-6.12) | 3.64 (.75-4.82) | 2.53 (1.90-3.38) | 1.64 (1.21-2.23) | 1.00 |
| Model 2[c] | 1.64 (1.48-1.82) | <0.001 | 2.76 (2.06-3.71) | 2.12 (1.58-2.5) | 1.64 (1.22-2.21) | 1.27 (0.93-1.73) | 1.00 |
| Model 3[d] | 1.64 (1.48-1.81) | <0.001 | 2.80 (2.09-3.76) | 2.12 (1.58-2.85) | 1.63 (1.21-2.20) | 1.26 (0.92-1.71) | 1.00 |
| Model 4[e] | 1.58 (1.42-1.75) | <0.001 | 2.54 (1.89-3.41) | 1.94 (1.33-2.62) | 1.51 (1.12-2.05) | 1.20 (0.88-1.64) | 1.00 |
| >30 kg/m² | (n=715) | | (n=76) | (n=78) | (n=130) | (n=182) | (n=249) |
| Model 1[b] | 1.61 (1.34-1.92) | <0.001 | 3.04 (1.91-4.83) | 2.49 (1.55-3.98) | 1.43 (0.88-2.31) | 1.31 (0.85-2.03) | 1.00 |
| Model 2[c] | 1.49 (1.22-1.81) | <0.001 | 2.25 (1.39-3.64) | 1.73 (1.05-2.83) | 0.95 (0.57-1.58) | 0.98 (0.62-1.53) | 1.00 |
| Model 3[d] | 1.48 (1.22-1.80) | <0.001 | 2.28 (1.41-3.69) | 1.76 (1.07-2.89) | 0.94 (0.57-1.57) | 0.98 (0.62-1.54) | 1.00 |
| Model 4[e] | 1.39 (1.14-1.70) | 0.001 | 1.97 (1.21-3.21) | 1.5 (1.01-2.72) | 0.88 (0.53-1.46) | 0.95 (0.61-1.49) | 1.00 |

Cox proportional hazard regression analysis to assess the association of UCE with 5-year survival.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs. non-trauma).

**Table ST2A. Logistic regression analyses of in-hospital mortality in patients below and above median age**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | | | Q1 | Q2 | Q3 | Q4 | Q5 |
| | OR (95% CI) | *P* | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | Reference |
| <62 yr | (n=3,089) | | (n=453) | (n=466) | (n=505) | (n=699) | (n=966) |
| Model 1[b] | 1.57 (1.40-1.76) | <0.001 | 3.56 (2.60-4.88) | 2.22 (1.59-3.11) | 1.60 (1.13-2.27) | 1.33 (0.95-1.86) | 1.00 |
| Model 2[c] | 1.53 (1.36-1.73) | <0.001 | 3.29 (2,40-4.53) | 1.97 (1.40-2.77) | 1.42 (0.99-2.02) | 1.25 (0.89-1.74) | 1.00 |
| Model 3[d] | 1.55 (1.37-1.75) | <0.001 | 3.28 (2.38-4.52) | 1.94 (1.38-2.73) | 1.43 (1.00-2.04) | 1.26 (0.90-1.76) | 1.00 |
| Model 4[e] | 1.61 (1.41-1.84) | <0.001 | 3.64 (2.58-5.14) | 2.13 (1.49-3.05) | 1.54 (1.07-2.22) | 1.32 (0.94-1.85) | 1.00 |
| Model 5[f] | 1.33 (1.16-1.53) | <0.001 | 2.27 (1.58-3.26) | 1.62 (1.11-2.35) | 1.15 (0.78-1.69) | 1.12 (0.79-1.59) | 1.00 |
| >62 yr | (n=3,062) | | (n=775) | (n=771) | (n=703) | (n=541) | (n=272) |
| Model 1[b] | 1.96 (1.71-2.25) | <0.001 | 3.49 (2.39-5.10) | 1.64 (1.11-2.42) | 1.15 (0.77-1.73) | 1.04 (0.68-1.59) | 1.00 |
| Model 2[c] | 1.86 (1.62-2.14) | <0.001 | 2.94 (2.00-4.34) | 1.39 (0.93-2.07) | 1.01 (0.67-1.53) | 0.97 (0.63-1.49) | 1.00 |
| Model 3[d] | 1.76 (1.53-2.03) | <0.001 | 2.76 (1.86-4.07) | 1.37 (0.92-2.05) | 1.02 (0.67-1.54) | 0.98 (0.64-1.51) | 1.00 |
| Model 4[e] | 1.82 (1.55-2.10) | <0.001 | 2.91 (1.91-4.41) | 1.44 (0.94-2.19) | 1.05 (0.69-1.61) | 1.01 (0.65-1.55) | 1.00 |
| Model 5[f] | 1.63 (1.40-1.91) | <0.001 | 2.45 (1.59-3.77) | 1.27 (0.82-1.97) | 0.98 (0.63-1.50) | 0.98(0.63-1.53) | 1.00 |

Multivariable logistic regression to assess the association of UCE with in-hospital mortality.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI)

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs non-trauma)

**Table ST2B. Cox proportional hazard regression analyses for 5-year mortality in patients below and above median age**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | | | Q1 | Q2 | Q3 | Q4 | Q5 |
| | HR (95% CI) | *P* | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | Reference |
| <62 y | (n=2,687) | | (n=344) | (n=389) | (n=442) | (n=625) | (n=887) |
| Model 1[b] | 1.69 (1.53-1.86) | <0.001 | 3.42 (2.60-4.50) | 2.80 (2.13-3.68) | 2.13 (1.61-2.82) | 1.43 (1.08-1.90) | 1.00 |
| Model 2[c] | 1.63 (1.47-1.81) | <0.001 | 2.94 (2.23-3.87) | 2.27 (1.72-3.00) | 1.70 (1.28-2.26) | 1.26 (0.95-1.68) | 1.00 |
| Model 3[d] | 1.59 (1.43-1.76) | <0.001 | 2.86 (2.17-3.77) | 2.28 (1.73-3.00) | 1.67 (1.25-2.22) | 1.25 (0.94-1.66) | 1.00 |
| Model 4[e] | 1.57 (1.41-1.75) | <0.001 | 2.77 (2.06-3.72) | 2.20 (1.65-2.96) | 1.63 (1.21-2.19) | 1.23 (0.92-1.65) | 1.00 |
| Model 5[f] | 1.49 (1.33-1.68) | <0.001 | 2.40 (1.77-3.26) | 1.96 (1.46-2.64) | 1.46 (1.08-1.96) | 1.14 (0.86-1.53) | 1.00 |
| >62y | (n=2,424) | | (n=506) | (n=617) | (n=598) | (n=467) | (n=236) |
| Model 1[b] | 1.58 (1.44-1.74) | <0.001 | 2.53 (1.93-3.33) | 1.78 (1.36-2.34) | 1.45 (1.10-1.92) | 1.20 (0.90-1.61) | 1.00 |
| Model 2[c] | 1.50 (1.36-1.66) | <0.001 | 2.19 (1.66-2.89) | 1.55 (1.17-2.05) | 1.30 (0.98-1.73) | 1.12 (0.84-1.51) | 1.00 |
| Model 3[d] | 1.51 (1.37-1.68) | <0.001 | 2.22 (1.68-2.93) | 1.55 (1.18-2.05) | 1.30 (0.98-1.72) | 1.12 (0.83-1.50) | 1.00 |
| Model 4[e] | 1.53 (1.38-1.70) | <0.001 | 2.24 (1.68-2.99) | 1.57 (1.18-2.09) | 1.30 (0.98-1.74) | 1.12 (0.83-1.51) | 1.00 |
| Model 5[f] | 1.50 (1.34-1.67) | <0.001 | 2.13 (1.59-2.86) | 1.50 (1.12-2.00) | 1.26 (0.95-1.69) | 1.11 (0.82-1.49) | 1.00 |

Cox proportional hazard regression analysis to assess the association of UCE with 5-year survival.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV).

**Table ST3A. Logistic regression analyses of in-hospital mortality in patients with and without acute kidney injury**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | | | Q1 | Q2 | Q3 | Q4 | Q5 |
| | OR (95% CI) | *P* | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | Reference |
| No AKI | (n=4,442) | | (n=689) | (n=823) | (n=903) | (n=1,007) | (n=1,020) |
| Model 1[b] | 1.69 (1.51-1.89) | <0.001 | 4.09 (3.05-5.49) | 2.60 (1.93-3.50) | 1.61 (1.18-2.21) | 1.50 (1.10-2.05) | 1.00 |
| Model 2[c] | 1.56 (1.39-1.76) | <0.001 | 3.23 (2.38-4.40) | 2.00 (1.46-2.74) | 1.28 (0.92-1.77) | 1.31 (0.96-1.79) | 1.00 |
| Model 3[d] | 1.62 (1.44-1.83) | <0.001 | 3.39 (2.48-4.62) | 2.06 (1.50-2.81) | 1.32 (0.95-1.82) | 1.33 (0.97-1.83) | 1.00 |
| Model 4[e] | 1.69 (1.49-1.93) | <0.001 | 3.83 (2.76-5.32) | 2.29 (1.65-3.20) | 1.42 (1.01-1.93) | 1.41 (1.02-1.93) | 1.00 |
| Model 5[f] | 1.48 (1.29-1.69) | <0.001 | 2.78 (1.97-3.93) | 1.78 (1.26-2.51) | 1.18 (0.83-1.66) | 1.27 (0.91-1.77) | 1.00 |
| AKI | (n=1,709) | | (n=539) | (n=414) | (n=305) | (n=233) | (n=218) |
| Model 1[b] | 1.63 (1.41-1.88) | <0.001 | 2.78 (1.90-4.07) | 1.23 (0.82-1.86) | 1.22 (0.79-1.88) | 0.95 (0.59-1.53) | 1.00 |
| Model 2[c] | 1.52 (1.31-1.76) | <0.001 | 2.15 (1.45-3.19) | 0.97 (0.63-1.48) | 0.98 (0.63-1.53) | 0.82 (0.50-1.33) | 1.00 |
| Model 3[d] | 1.52 (1.31-1.76) | <0.001 | 2.15 (1.45-3.19) | 0.97 (0.64-1.49) | 0.98 (0.63-1.53) | 0.82 (0.51-1.33) | 1.00 |
| Model 4[e] | 1.52 (1.30-1.78) | <0.001 | 2.17 (1.43-3.29) | 0.98 (0.63-1.52) | 0.99 (0.63-1.56) | 0.82 (0.51-1.33) | 1.00 |
| Model 5[f] | 1.36 (1.15-1.60) | <0.001 | 1.72 (1.11-2.66) | 0.88 (0.49-1.25) | 0.80 (0.56-1.39) | 0.76 (0.46-1.25) | 1.00 |

Multivariable logistic regression to assess the association of UCE with in-hospital mortality.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI)

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs. non-trauma).

**Table ST3B. Cox proportional hazard regression analyses for 5-year mortality in patients with and without acute kidney injury**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | | | Q1 | Q2 | Q3 | Q4 | Q5 |
| | HR (95% CI) | *P* | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | Reference |
| No AKI | (n=3,855) | | (n=522) | (n=684) | (n=802) | (n=901) | (n=946) |
| Model 1[b] | 1.86 (1.73-2.00) | <0.001 | 4.62 (3.74-5.70) | 3.40 (2.76-4.18) | 2.52 (2.04-3.11) | 1.68 (1.35-2.09) | 1.00 |
| Model 2[c] | 1.64 (1.51-1.79) | <0.001 | 2.97 (2.39-3.70) | 2.04 (1.64-2.54) | 1.60 (1.28-1.98) | 1.26 (1.01-1.57) | 1.00 |
| Model 3[d] | 1.62 (1.49-1.76) | <0.001 | 2.88 (2.31-3.59) | 2.01 (1.61-2.50) | 1.56 (1.26-1.94) | 1.25 (1.00-1.56) | 1.00 |
| Model 4[e] | 1.61 (1.47-1.76) | <0.001 | 2.84 (2.25-3.9) | 1.98 (1.58-2.49) | 1.55 (1.24-1.94) | 1.24 (0.99-1.55) | 1.00 |
| Model 5[f] | 1.55 (1.41-1.69) | <0.001 | 2.54 (2.00-3.21) | 1.81 (1.43-2.28) | 1.41 (1.13-1.77) | 1.16 (0.93-1.46) | 1.00 |
| AKI | (n=1,256) | | (n=328) | (n=322) | (n=238) | (n=191) | (n=177) |
| Model 1[b] | 1.65 (1.43-1.90) | <0.001 | 3.08 (2.05-4.64) | 2.25 (1.48-3.42) | 1.86 (1.19-2.90) | 1.53 (0.95-2.47) | 1.00 |
| Model 2[c] | 1.50 (1.29-1.74) | <0.001 | 2.09 (1.37-3.19) | 1.55 (1.01-2.39) | 1.34 (0.85-2.11) | 1.23 (0.76-1.98) | 1.00 |
| Model 3[d] | 1.50 (1.29-1.75) | <0.001 | 2.10 (1.38-3.19) | 1.55 (1.01-2.38) | 1.34 (0.85-2.11) | 1.23 (0.76-1.98) | 1.00 |
| Model 4[e] | 1.54 (1.31-1.80) | <0.001 | 2.18 (1.40-3.40) | 1.61 (1.03-2.52) | 1.37 (0.86-2.18) | 1.24 (0.77-2.00) | 1.00 |
| Model 5[f] | 1.52 (1.29-1.78) | <0.001 | 2.14 (1.36-3.38) | 1.63 (1.03-2.57) | 1.38 (0.86-2.21) | 1.25 (0.77-2.04) | 1.00 |

Cox proportional hazard regression analysis to assess the association of UCE with 5-year survival.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs. non-trauma).

**Table ST4A. Logistic regression analyses of in-hospital mortality in trauma patients**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | (n=537) | | **Q1** (n=35) | **Q2** (n=48) | **Q3** (n=58) | **Q4** (n=117) | **Q5** (n=279) |
| | OR (95% CI) | *P* | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | Reference |
| Model 1[b] | 1.92 (1.40-2.65) | <0.001 | 5.22 (2.03-13.42) | 2.05 (0.71-5.92) | 4.59 (2.02-10.44) | 2.01 (0.91-4.44) | 1.00 |
| Model 2[c] | 1.34 (0.94-1.93) | 0.110 | 1.83 (0.61-5.50) | 0.88 (0.28-2.81) | 2.44 (0.99-6.01) | 1.62 (0.72-3.66) | 1.00 |
| Model 3[d] | 1.29 (0.90-1.85) | 0.168 | 1.39 (0.45-4.33) | 0.90 (0.28-2.90) | 2.38 (0.96-5.89) | 1.73 (0.76-3.92) | 1.00 |
| Model 4[e] | 1.19 (0.80-1.77) | 0.388 | 1.04 (0.30-3.62) | 0.72 (0.21-2.47) | 2.10 (0.82-5.37) | 1.56 (0.67-3.60) | 1.00 |
| Model 5[f] | 1.10 (0.71-1.71) | 0.658 | 0.80 (0.20-3.14) | 0.59 (0.17-2.13) | 1.79 (0.67-4.80) | 1.41 (0.60-3.34) | 1.00 |

Multivariable logistic regression to assess the association of UCE with in-hospital mortality.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for BMI (body mass index).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV).

**Table ST4B. Cox proportional hazard regression analyses for 5-year mortality in trauma patients**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | (n=485) | | **Q1** (n=27) | **Q2** (n=43) | **Q3** (n=46) | **Q4** (n=105) | **Q5** (n=264) |
| | HR (95% CI) | *P* | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | Reference |
| Model 1[b] | 3.33 (2.38-4.67) | <0.001 | 21.06 (9.47-46.80) | 8.53 (3.82-19.06) | 5.21 (2.16-12.59) | 1.66 (0.64-4.28) | 1.00 |
| Model 2[c] | 2.14 (1.44-3.16) | <0.001 | 6.68 (2.68-16.63) | 2.86 (1.15-7.06) | 2.42 (0.95-6.16) | 1.10 (0.42-2.90) | 1.00 |
| Model 3[d] | 2.09 (1.41-3.10) | <0.001 | 6.27 (2.48-15.82) | 2.94 (1.19-7.27) | 2.46 (0.97-6.25) | 1.14 (0.43-3.02) | 1.00 |
| Model 4[e] | 2.23 (1.47-3.38) | <0.001 | 7.67 (2.81-20.91) | 3.49 (1.33-9.18) | 2.63 (1.03-6.73) | 1.23 (0.46-3.30) | 1.00 |
| Model 5[f] | 2.21 (1.46-3.37) | <0.001 | 7.58(2.74-20.98) | 3.49 (1.32-9.19) | 2.62 (1.02-6.71) | 1.23 (0.46-3.29) | 1.00 |

Cox proportional hazard regression analysis to assess the association of UCE with 5-year survival.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV).

**Table ST5A. Logistic regression analyses of in-hospital mortality in complete cases**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | (n=4,336) | | **Q1** (n=901) | **Q2** (n=860) | **Q3** (n=868) | **Q4** (n=897) | **Q5** (n=810) |
| | OR (95% CI) | *P* | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | Reference |
| Model 1[b] | 1.91 (1.72-2.13) | <0.001 | 4.39 (3.32-5.81) | 2.17 (1.61-2.92) | 1.44 (1.05-1.96) | 1.32 (0.97-1.82) | 1.00 |
| Model 2[c] | 1.82 (1.63-2.04) | <0.001 | 3.67 (2.74-4.92) | 1.79 (1.31-2.44) | 1.23 (0.89-1.69) | 1.21 (0.88-1.66) | 1.00 |
| Model 3[d] | 1.81 (1.61-2.02) | <0.001 | 3.53 (2.63-4.74) | 1.76 (1.29-2.41) | 1.23 (0.89-1.70) | 1.22 (0.89-1.69) | 1.00 |
| Model 4[e] | 1.86 (1.64-2.10) | <0.001 | 3.77 (2.76-5.15) | 1.88 (1.35-2.60) | 1.28 (0.92-1.78) | 1.26 (0.91-1.74) | 1.00 |
| Model 5[f] | 1.56 (1.38-1.77) | <0.001 | 2.59 (1.87-3.59) | 1.46 (1.03-2.05) | 1.02 (0.72-1.43) | 1.14 (0.81-1.59) | 1.00 |

Multivariable logistic regression to assess the association of UCE with in-hospital mortality.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI)

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs non-trauma).

**Table ST5B. Cox proportional hazard regression analyses for 5-year mortality in complete cases**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | (n=3,626) | | **Q1** (n=628) | **Q2** (n=708) | **Q3** (n=760) | **Q4** (n=793) | **Q5** (n=737) |
| | HR (95% CI) | *P* | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | Reference |
| Model 1[b] | 1.76 (1.66-1.88) | <0.001 | 3.98 (3.17-4.99) | 3.14 (2.50-3.95) | 2.13 (1.68-2.70) | 1.48 (1.15-1.90) | 1.00 |
| Model 2[c] | 1.56 (1.45-1.68) | <0.001 | 2.53 (2.00-3.22) | 1.94 (1.53-2.47) | 1.43 (1.12-1.83) | 1.16 (0.90-1.49) | 1.00 |
| Model 3[d] | 1.55 (1.45-1.67) | <0.001 | 2.55 (2.01-3.24) | 1.94 (1.52-2.46) | 1.42 (1.11-1.81) | 1.15 (0.89-1.48) | 1.00 |
| Model 4[e] | 1.59 (1.45-1.75) | <0.001 | 2.53 (1.97-3.25) | 1.92 (1.50-2.47) | 1.41 (1.10-1.81) | 1.14 (0.89-1.48) | 1.00 |
| Model 5[f] | 1.53 (1.39-1.68) | <0.001 | 2.30 (1.79-2.96) | 1.77 (1.38-2.28) | 1.32 (1.03-1.69) | 1.10 (0.86-1.42) | 1.00 |

Cox proportional hazard regression analysis to assess the association of UCE with 5-year survival.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs non-trauma).

**Table ST6A. Logistic regression analyses of in-hospital mortality with adjustment for BSA**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | (n=6,151) | | **Q1** (n=1,228) | **Q2** (n=1,237) | **Q3** (n=1,208) | **Q4** (n=1,240) | **Q5** (n=1,238) |
| | OR (95% CI) | *P* | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | Reference |
| Model 1[b] | 1.81 (1.66-1.97) | <0.001 | 4.34 (3.46-5.45) | 2.24 (1.77-2.85) | 1.58 (1.23-2.03) | 1.32 (1.02-1.71) | 1.00 |
| Model 2[c] | 1.67 (1.52-1.83) | <0.001 | 3.32 (2.61-4.20) | 1.69 (1.32-2.17) | 1.22 (0.94-1.59) | 1.14 (0.88-1.48) | 1.00 |
| Model 3[d] | 1.26 (1.11-1.35) | <0.001 | 1.82 (1.35-2.45) | 1.09 (0.83-1.45) | 0.89 (0.66-1.18) | 0.93 (0.71-1.22) | 1.00 |
| Model 4[e] | 1.32 (1.16-1.50) | <0.001 | 2.05 (1.49-2.82) | 1.21 (0.90-1.63) | 0.96 (0.72-1.28) | 0.98 (0.74-1.28) | 1.00 |
| Model 5[f] | 1.35 (1.18-1.55) | <0.001 | 2.12 (1.53-2.96) | 1.26 (0.93-1.72) | 0.98 (0.73-1.31) | 1.00 (0.76-1.33) | 1.00 |

Multivariable logistic regression to assess the association of UCE with in-hospital mortality.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body surface area (BSA).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs.non-trauma).

**Table ST6B. Cox proportional hazard regression analyses for 5-year mortality with adjustment for BSA**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | (n=5,111) | | **Q1** (n=850) | **Q2** (n=1,006) | **Q3** (1,040) | **Q4** (n=1,092) | **Q5** (n=1,123) |
| | HR (95% CI) | *P* | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | Reference |
| Model 1[b] | 1.76 (1.66-1.88) | <0.001 | 4.03 (3.35-4.84) | 3.02 (2.51-3.64) | 2.36 (1.95-2.86) | 1.65 (1.35-2.01) | 1.00 |
| Model 2[c] | 1.56 (1.45-1.68) | <0.001 | 2.58 (2.13-3.13) | 1.88 (1.55-2.28) | 1.53 (1.26-1.87) | 1.25 (1.02-1.53) | 1.00 |
| Model 3[d] | 1.81 (1.64-1.99) | <0.001 | 3.13 (2.46-3.98) | 2.16 (1.73-2.70) | 1.70 (1.38-2.10) | 1.34 (1.09-1.65) | 1.00 |
| Model 4[e] | 1.81 (1.64-2.01) | <0.001 | 3.09 (2.39-3.97) | 2.14 (1.69-2.70) | 1.69 (1.36-2.10) | 1.33 (1.08-1.64) | 1.00 |
| Model 5[f] | 1.80 (1.62-2.00) | <0.001 | 2.97 (2.31-3.84) | 2.06 (1.63-2.60) | 1.61 (1.30-2.01) | 1.29 (1.04-1.59) | 1.00 |

Cox proportional hazard regression analysis to assess the association of UCE with 5-year survival.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body surface area (BSA).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs. non-trauma).

**Table ST7. Mean UCE in short-term surviving and non-surviving trauma patients with or without rhabdomyolysis**

| | Survivors | N | Non-survivors | N | **P** |
|---|---|---|---|---|---|
| CK ≥1500 U/l | 17.1 (5.5) | 137 | 13.8 (5.5) | 12 | <0.001 |
| CK < 1500 U/l | 14.7 (5.8) | 348 | 12.0 (5.5) | 40 | <0.001 |

Mean (SD) UCE in short-term surviving and non-surviving traumapatients with or without rhabdomyolysis. UCE is depicted in 24-h. Rhabdomyolysis is defined as a CK of ≥1500 U/l.

**Table ST8A. Logistic regression analyses of in-hospital mortality with adjustment for mCC**

| | **UCE**[a] | | **UCE sex-stratified quintiles** | | | | |
|---|---|---|---|---|---|---|---|
| | (n=6,151) | | **Q1** (n=1,228) | **Q2** (n=1,237) | **Q3** (n=1,208) | **Q4** (n=1,240) | **Q5** (n=1,238) |
| | OR (95% CI) | *P* | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | Reference |
| Model 1[b] | 1.81 (1.66-1.97) | <0.001 | 4.34 (3.46-5.45) | 2.24 (1.77-2.85) | 1.58 (1.23-2.03) | 1.32 (1.02-1.71) | 1.00 |
| Model 2[c] | 1.67 (1.52-1.83) | <0.001 | 3.32 (2.61-4.20) | 1.69 (1.32-2.17) | 1.22 (0.94-1.59) | 1.14 (0.88-1.48) | 1.00 |
| Model 3[d] | 1.26 (1.11-1.35) | <0.001 | 1.82 (1.35-2.45) | 1.09 (0.83-1.45) | 0.89 (0.66-1.18) | 0.93 (0.71-1.22) | 1.00 |
| Model 4[e] | 1.32 (1.16-1.50) | <0.001 | 2.05 (1.49-2.82) | 1.21 (0.90-1.63) | 0.96 (0.72-1.28) | 0.98 (0.74-1.28) | 1.00 |
| Model 5[f] | 1.35 (1.18-1.55) | <0.001 | 2.12 (1.53-2.96) | 1.26 (0.93-1.72) | 0.98 (0.73-1.31) | 1.00 (0.76-1.33) | 1.00 |

Multivariable logistic regression to assess the association of UCE with in-hospital mortality.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (mCC).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs.non-trauma).

**Table ST8B. Cox proportional hazard regression analyses for 5-year mortality with adjustment for mCC**

| | **UCE**[a] | | **UCE sex-stratified quintiles** | | | | |
|---|---|---|---|---|---|---|---|
| | (n=5,111) | | **Q1** (n=850) | **Q2** (n=1,006) | **Q3** (1,040) | **Q4** (n=1,092) | **Q5** (n=1,123) |
| | HR (95% CI) | *P* | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | Reference |
| Model 1[b] | 1.76 (1.66-1.88) | <0.001 | 4.03 (3.35-4.84) | 3.02 (2.51-3.64) | 2.36 (1.95-2.86) | 1.65 (1.35-2.01) | 1.00 |
| Model 2[c] | 1.56 (1.45-1.68) | <0.001 | 2.58 (2.13-3.13) | 1.88 (1.55-2.28) | 1.53 (1.26-1.87) | 1.25 (1.02-1.53) | 1.00 |
| Model 3[d] | 1.81 (1.64-1.99) | <0.001 | 3.13 (2.46-3.98) | 2.16 (1.73-2.70) | 1.70 (1.38-2.10) | 1.34 (1.09-1.65) | 1.00 |
| Model 4[e] | 1.81 (1.64-2.01) | <0.001 | 3.09 (2.39-3.97) | 2.14 (1.69-2.70) | 1.69 (1.36-2.10) | 1.33 (1.08-1.64) | 1.00 |
| Model 5[f] | 1.80 (1.62-2.00) | <0.001 | 2.97 (2.31-3.84) | 2.06 (1.63-2.60) | 1.61 (1.30-2.01) | 1.29 (1.04-1.59) | 1.00 |

Cox proportional hazard regression analysis to assess the association of UCE with 5-year survival.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (mCC).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs. non-trauma).

**Table ST9A. Logistic regression analyses of in-hospital mortality with adjustment for changes in serum creatinine >26.5 umol/L**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | | | Q1 | Q2 | Q3 | Q4 | Q5 |
| | OR (95% CI) | *P* | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | Reference |
| >26.5 umol/L | (n=1,386) | | (n=261) | (n=215) | (n=184) | (n=166) | (n=1331) |
| Model 1[b] | 1.92 (1.63-2.28) | <0.001 | 4.05 (2.58-6.34) | 1.91 (1.19-3.08) | 1.56 (0.94-2.59) | 1.18 (0.69-2.02) | 1.00 |
| Model 2[c] | 1.72 (1.45-2.05) | <0.001 | 2.88 (1.80-4.60) | 1.42 (0.87-2.33) | 1.19 (0.71-2.01) | 1.02 (0.59-1.76) | 1.00 |
| Model 3[d] | 1.70 (1.42-2.03) | <0.001 | 2.76 (1.72-4.43) | 1.38 (0.84-2.27) | 1.16 (0.69-1.96) | 1.01 (0.59-1.74) | 1.00 |
| Model 4[e] | 1.75 (1.44-2.12) | <0.001 | 2.96 (1.77-4.93) | 1.47 (0.87-2.46) | 1.21 (0.71-2.07) | 1.03 (0.60-1.79) | 1.00 |
| Model 5[f] | 1.60 (1.31-1.96) | <0.001 | 2.41 (1.42-4.09) | 1.31 (0.77-2.23) | 1.07 (0.62-1.84) | 0.94 (0.54-1.65) | 1.00 |
| ≤26.5 umol/L | (n=4,765) | | (n=856) | (n=923) | (n=956) | (n=1010) | (n=1020) |
| Model 1[b] | 1.71 (1.55-1.89) | <0.001 | 4.15 (3.19-5.42) | 2.28 (1.73-3.01) | 1.55 (1.16-2.08) | 1.36 (1.02-1.83) | 1.00 |
| Model 2[c] | 1.60 (1.44-1.79) | <0.001 | 3.34 (2.53-4.41) | 1.79 (1.34-2.40) | 1.25 (0.92-1.69) | 1.20 (0.89-1.61) | 1.00 |
| Model 3[d] | 1.66 (1.49-1.85) | <0.001 | 3.48 (2.63-4.60) | 1.85 (1.38-2.49) | 1.32-0.97-1.78) | 1.23 (0.92-1.67) | 1.00 |
| Model 4[e] | 1.72 (1.53-1.93) | <0.001 | 3.80 (2.92-5.11) | 2.01 (1.48-2.73) | 1.39 (1.02-1.90) | 1.28 (0.95-1.73) | 1.00 |
| Model 5[f] | 1.48 (1.31-1.68) | 0.02 | 2.70 (1.98-3.69) | 1.55 (1.13-2.14) | 1.14 (0.82-1.57) | 1.15 (0.84-1.58) | 1.00 |

Multivariable logistic regression to assess the association of UCE with in-hospital mortality.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

e Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI).

f Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs non-trauma).

**Table ST9B. Cox proportional hazard regression analyses for 5-year mortality with adjustment for changes in serum creatinine >26.5 umol/L**

| | UCE[a] | | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|---|---|
| | | | Q1 | Q2 | Q3 | Q4 | Q5 |
| | HR (95% CI) | *P* | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | Reference |
| >26.5 umol/L | (n=1,069) | | (n=522) | (n=684) | (n=802) | (n=901) | (n=946) |
| Model 1[b] | 1.59 (1.38-1.83) | <0.001 | 2.95 (1.96-4.46) | 2.53 (1.67-3.83) | 1.86 (1.20-2.90) | 1.47 (0.92-2.33) | 1.00 |
| Model 2[c] | 1.36 (1.17-1.58) | <0.001 | 1.76 (1.15-2.70) | 1.60 (1.04-2.46) | 1.22 (0.78-1.92) | 1.14 (0.72-183) | 1.00 |
| Model 3[d] | 1.34 (1.15-1.56) | <0.001 | 1.69 (1.10-2.61) | 1.56 (1.01-2.40) | 1.19 (0.76-1.88) | 1.14 (0.71_1.81) | 1.00 |
| Model 4[e] | 1.42 (1.20-1.68) | <0.001 | 1.95 (1.23-3.08) | 1.76 (1.12-2.77) | 1.31 (0.92-2.08) | 1.19 (0.75-1.91) | 1.00 |
| Model 5[f] | 1.40 (1.18-1.66) | <0.001 | 1.88 (1.17-3.01) | 1.79 (1.13-2.84) | 1.28 (0.79-2.06) | 1.19 (0.74-1.92) | 1.00 |
| ≤26.5 umol/L | (n=4,042) | | (n=328) | (n=322) | (n=238) | (n=191) | (n=177) |
| Model 1[b] | 1.83 (1.70-1.97) | <0.001 | 4.44 (3.61-5.46) | 3.16 (2.57-3.88) | 2.49 (2.02-3.08) | 1.69 (1.36-2.11) | 1.00 |
| Model 2[c] | 1.64 (1.52-1.78) | <0.001 | 2.93 (2.36-3.64) | 1.96 (1.58-2.44) | 1.62 (1.31-2.02) | 1.28 (1.03-1.61) | 1.00 |
| Model 3[d] | 1.61 (1.48-1.74) | <0.001 | 2.82 (2.27-3.50) | 1.91 (1.54-2.38) | 1.57 (1.26-1.96) | 1.26 (1.01-1.58) | 1.00 |
| Model 4[e] | 1.58 (1.45-1.72) | 0.015 | 2.70 (2.14-3.39) | 1.83 (1.46-2.31) | 1.53 (1.23-1.91) | 1.24 (0.99-1.55) | 1.00 |
| Model 5[f] | 1.50 (1.38-1.65) | 0.03 | 2.35 (1.87-2.97) | 1.64 (1.30-2.06) | 1.48 (1.10-1.73) | 1.15 (0.92-1.44) | 1.00 |

Cox proportional hazard regression analysis to assess the association of UCE with 5-year survival.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs non-trauma).

**Table ST10A. Logistic regression analyses of in-hospital mortality with UCE/kg**

| | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|
| | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** |
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | Reference |
| UCE/kg | (n=950) | (n=994) | (n=1064) | (n=1057) | (n=913) |
| Model 1[b] | 5.03 (3.83-6.60) | 2.25 (1.69-3.00) | 1.46 (1.08-1.97) | 1.37 (1.01-1.85) | 1.00 |
| Model 2[c] | 3.86 (2.89-5.15) | 1.68 (1.24-2.28) | 1.13 (0.83-1.55) | 1.17 (0.86-1.59) | 1.00 |
| Model 3[d] | 3.55 (2.65-4.77) | 1.60 (1.18-2.18) | 1.11 (0.81-1.53) | 1.16 (0.85-1.59) | 1.00 |
| Model 4[e] | 3.66 (2.73-4.92) | 1.64 (1.20-2.23) | 1.14 (0.83-1.56) | 1.18 (0.87-1.62) | 1.00 |
| Model 5[f] | 2.53 (1.86-3.45) | 1.24 (0.90-1.72) | 0.91 (0.66-1.27) | 1.09 (0.79-1.50) | 1.00 |
| UCE* | (n=992) | (n=994) | (n=992) | (n=1023) | (n=977) |
| Model 1[b] | 4.70 (3.61-6.13) | 2.25 (1.69-2.98) | 1.56 (1.16-2.10) | 1.43 (1.06-1.92) | 1.00 |
| Model 2[c] | 3.76 (2.85-4.95) | 1.77 (1.32-2.38) | 1.27 (0.94-1.73) | 1.26 (0.94-1.71) | 1.00 |
| Model 3[d] | 3.61 (2.73-4.77) | 1.76 (1.31-2.36) | 1.28 (0.94-1.74) | 1.29 (0.95-1.73) | 1.00 |
| Model 4[e] | 3.97 (2.96-5.33) | 1.92 (1.41-2.60) | 1.26 (1.00-1.85) | 1.33 (1.00-1.01) | 1.00 |
| Model 5[f] | 2.71 (2.00-3.70) | 1.48 (1.07-2.04) | 1.08 (0.78-1.50) | 1.19 (0.87-1.63) | 1.00 |

Multivariable logistic regression to assess the association of UCE with in-hospital mortality. *This analysis was only performed in patients with known baseline weight.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs non-trauma).

**Table ST10B. Cox proportional hazard regression analyses for 5-year mortality with UCE/kg**

| | UCE sex-stratified quintiles | | | | |
|---|---|---|---|---|---|
| | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** |
| | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | Reference |
| UCE/kg | (n=652) | (n=825) | (n=939) | (n=940) | (n=837) |
| Model 1[b] | 3.72 (3.03-4.58) | 2.37 (1.92-2.92) | 2.22 (1.80-2.73) | 1.36 (1.09-1.71) | 1.00 |
| Model 2[c] | 2.10 (1.69-2.62) | 1.22 (0.98-1.53) | 1.26 (1.01-.157) | 0.96 (0.77-1.21) | 1.00 |
| Model 3[d] | 2.20 (1.76-2.73) | 1.23 (1.00-1.57) | 1.27 (1.02-1.57) | 0.96 (0.77-1.21) | 1.00 |
| Model 4[e] | 2.30 (1.85-2.87) | 1.30 (1.04-1.63) | 1.31 (1.05-1.63) | 0.99 (0.79-1.24) | 1.00 |
| Model 5[f] | 2.06 (1.64-2.57) | 1.18 (0.94-1.48) | 1.21 (0.97-1.50) | 0.94 (0.75-1.18) | 1.00 |
| UCE* | (n=696) | (n=826) | (n=869) | (n=906) | (n=896) |
| Model 1[b] | 3.86 (3.13-4.74) | 3.02 (2.46-3.72) | 2.15 (1.73-2.66) | 1.53 (1.23-1.92) | 1.00 |
| Model 2[c] | 2.42 (1.94-3.00) | 1.84 (1.48-2.29) | 1.40 (1.12-1.75) | 1.17 (0.94-1.47) | 1.00 |
| Model 3[d] | 2.44 (1.96-3.03) | 1.83 (1.47-2.28) | 1.38 (1.11-1.73) | 1.17 (0.93-1.46) | 1.00 |
| Model 4[e] | 2.45 (1.95-3.08) | 1.84 (1.47-2.31) | 1.39 (1.11-1.74) | 1.17 (0.93-1.47) | 1.00 |
| Model 5[f] | 2.19 (1.74-2.76) | 1.67 (1.33-2.11) | 1.27 (1.01-1.60) | 1.10 (0.88-1.39) | 1.00 |

Cox proportional hazard regression analysis to assess the association of UCE with 5-year survival. *This analysis was only performed in patients with known baseline weight.

[a] UCE was entered as a continuous variable per 5 mmol/24h decrease.

[b] Model 1: Adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles.

[c] Model 2: Adjusted as for model 1, additionally adjusted for age.

[d] Model 3: Adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI).

[e] Model 4: Adjusted as for model 3, additionally adjusted for body mass index (BMI).

[f] Model 5: Adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs non-trauma).

## FIGURES

| Subgroup | Subjects | Events | OR (95%CI) | P interaction | P interaction* |
|---|---|---|---|---|---|
| Age | | | | 0.048 | 0.513 |
| ≤ 62 years | 3089 | 402 | 1.48 (1.33-1.65) | | |
| > 62 years | 3062 | 638 | 1.74 (1.54-1.97) | | |
| Sex | | | | <0.001 | 0.052 |
| Male | 3814 | 628 | 1.66 (1.51-1.82) | | |
| Female | 2337 | 412 | 2.51 (2.06-3.04) | | |
| Renal function | | | | 0.948 | 0.809 |
| ≤ 89 mL/min/1.73m² | 3075 | 691 | 1.62 (1.50-1.81) | | |
| > 89 mL/min/1.73m² | 3076 | 349 | 1.49 (1.32-1.68) | | |
| Body mass index** | | | | 0.004 | 0.133 |
| ≤ 30 kg/m² | 4121 | 646 | 1.72 (1.55-1.90) | | |
| > 30 kg/m² | 854 | 139 | 2.06 (1.66-2.56) | | |
| APACHE IV*** | | | | 0.961 | 0.887 |
| ≤ 59 | 2191 | 147 | 1.61 (1.33-1.96) | | |
| > 59 | 2251 | 583 | 1.50 (1.33-1.68) | | |
| Reason of admission | | | | 0.912 | 0.245 |
| Trauma | 537 | 52 | 1.61 (1.26-2.11) | | |
| Non-trauma | 5614 | 988 | 1.63 (1.50-1.78) | | |

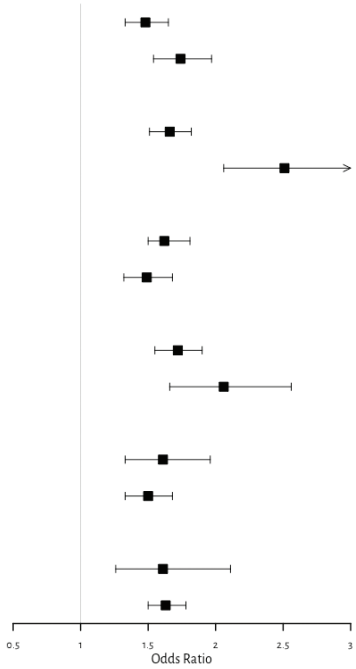


**Figure S1A. Stratified analysis of the association of UCE with short-term mortality stratified.**

Unadjusted ORs are shown. Interaction was tested both unadjusted and adjusted. Adjustments were made for sex, age, renal function, body mass index, severity of illness and reason of admission. Subgroups with and adjusted *P* interaction <0.05 were considered effect modifiers on the association of UCE with short-term mortality. *Adjusted *P* interaction. ** Data missing of 1,709 (28%) patients. *** Data missing of 1,176 (19%) patients.

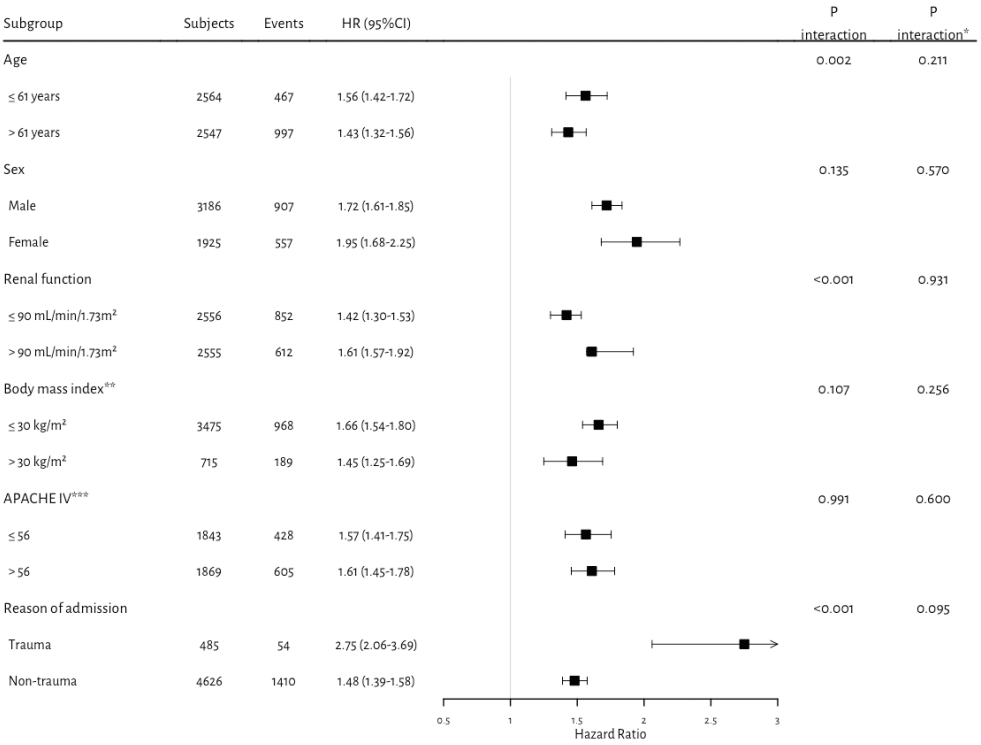


**Figure S1B. Stratified analysis of the association of UCE with long-term mortality stratified.**
Unadjusted ORs are shown. Interaction was tested both unadjusted and adjusted. Adjustments were made for sex, age, renal function, body mass index, severity of illness and reason of admission. Subgroups with an adjusted *P* interaction <0.05 were considered effect modifiers on the association of UCE with short-term mortality. *Adjusted *P* interaction. ** Data missing of 1,709 (28%) patients. *** Data missing of 1,176 (19%) patients.

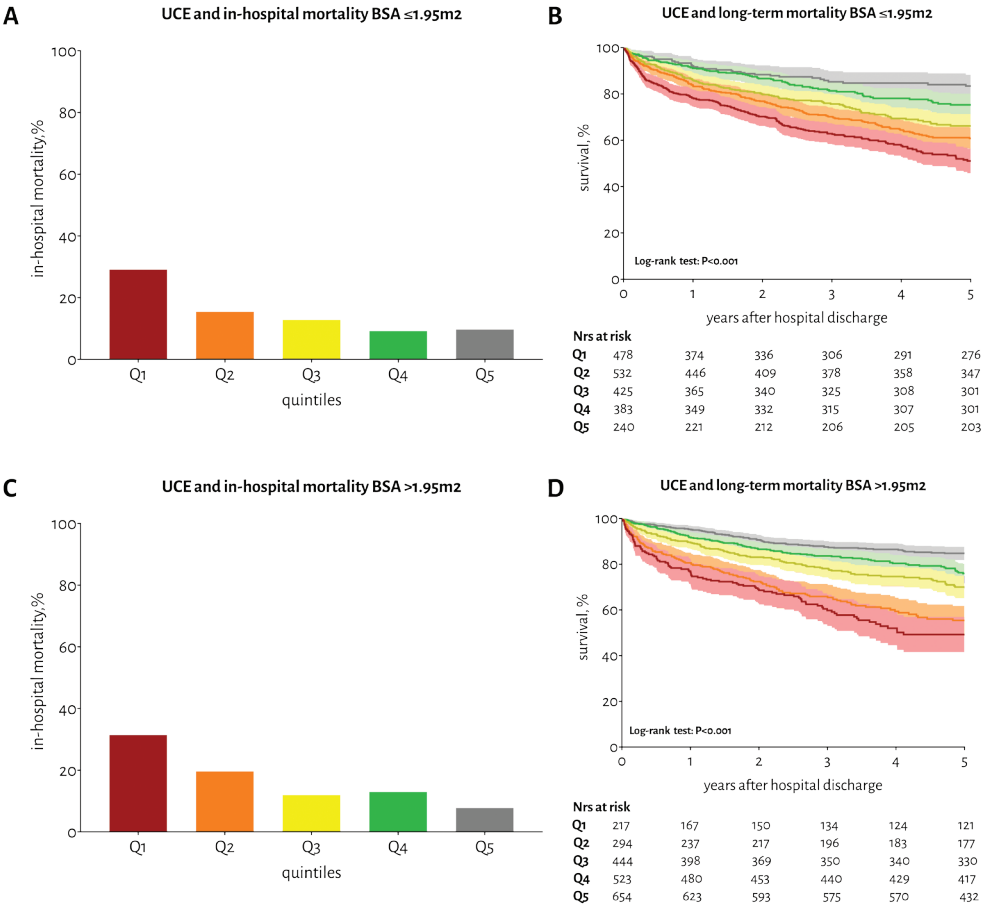


**Figure S2. Short- and long-term mortality as expressed in UCE quintiles for a subgroup of BSA.**

A/C. In-hospital mortality is depicted for the UCE quintiles in percentages. The first quintile represents the lowest quintile, the fifth quintile represents he highest quintile. Corresponding quintile cut-off values are shown in Table 1. In-hospital mortality increased when baseline UCE decreased in both BSA subgroups.

B/D. Kaplan-Meier curves for long-term mortality (with 95% CI) after hospital discharge. The colors of the quintiles correspond to colors as depicted in figure S3A/3C. The highest UCE quintile had the lowest long-term mortality, which rose with declining baseline UCE (log-rank test: $P < 0.001$).

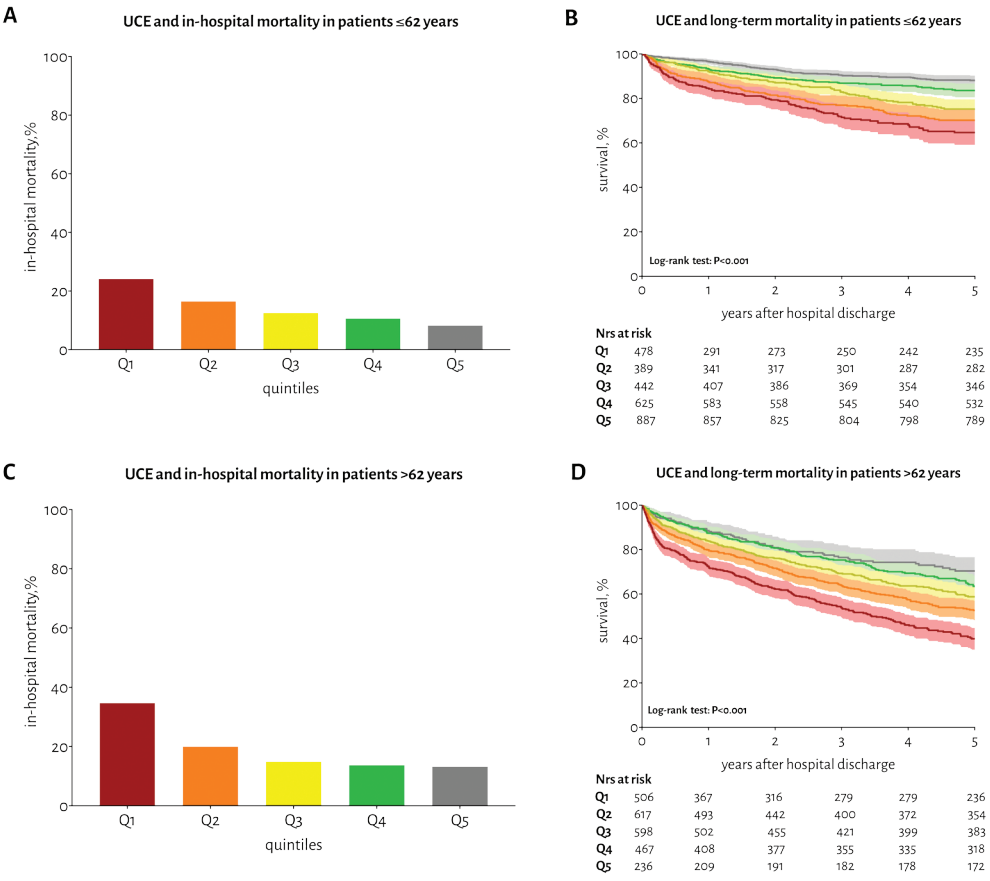


**Figure S3. Short- and long-term mortality as expressed in UCE quintiles for patients below and above median age.**
A/C. In-hospital mortality is depicted for the UCE quintiles in percentages. The first quintile represents the lowest quintile, the fifth quintile represents the highest quintile. Corresponding quintile cut-off values are shown in Table 1. In-hospital mortality increased when baseline UCE decreased for both age groups.
B/D. Kaplan-Meier curves for long-term mortality (with 95% CI) after hospital discharge. The colors of the quintiles correspond to colors as depicted in figure 4A/4C. The highest UCE quintile had the best long-term mortality, which declined with declining baseline UCE (log-rank test: $P < 0.001$). UCE was more discriminative in patients older than 62 years.

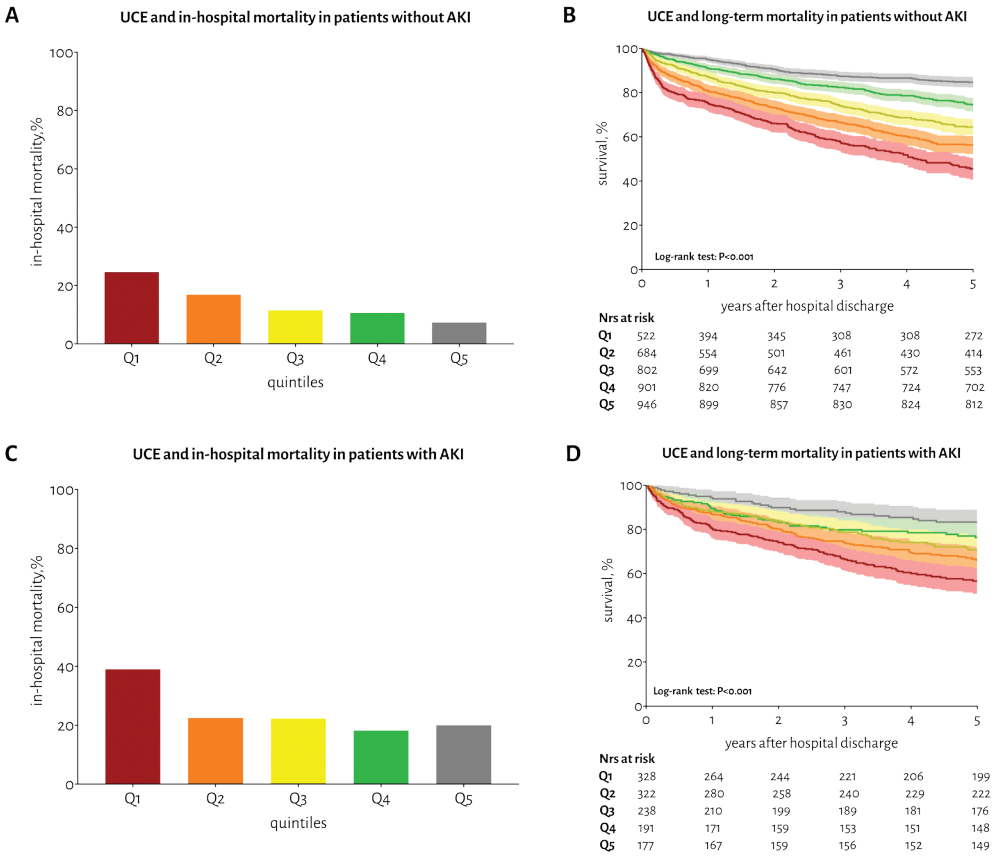


**Figure S4. Short- and long-term mortality as expressed in UCE quintiles for patients with and without acute kidney injury.**

A/C. In-hospital mortality is depicted for the UCE quintiles in percentages. The first quintile represents the lowest quintile, the fifth quintile represents he highest quintile. Corresponding quintile cut-off values are shown in Table 1. In-hospital mortality increased when baseline UCE decreased in both patients with and without AKI.

B/D. Kaplan-Meier curves for long-term mortality (with 95% CI) after hospital discharge. The colors of the quintiles correspond to colors as depicted in figure S5A/5C. The highest UCE quintile had the lowest long-term mortality, which rose with declining baseline UCE (log-rank test: $P < 0.001$). UCE discriminated better in patients without AKI than patients with AKI.

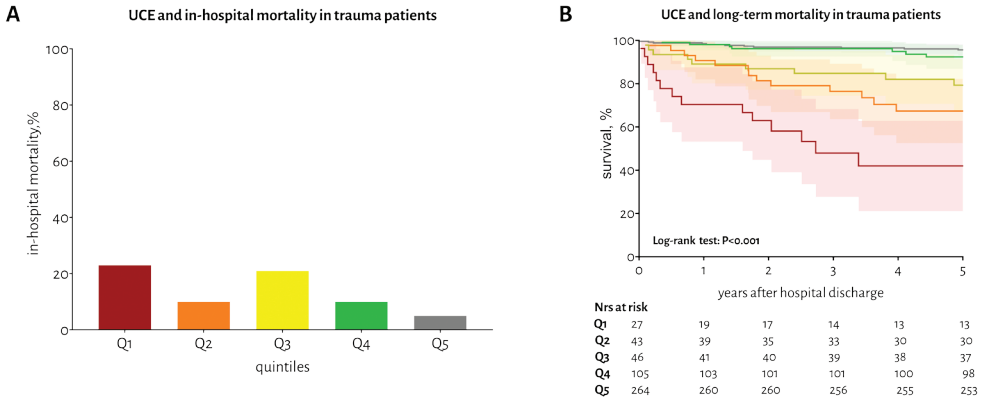


**Figure S5. Short- and long-term mortality as expressed in UCE quintiles for trauma patients.**

A. In-hospital mortality is depicted for the UCE quintiles in percentages. The first quintile represents the lowest quintile, the fifth quintile represents the highest quintile. Corresponding quintile cut-off values are shown in Table 1. In-hospital mortality was highest in trauma patients in the first and third UCE quintile.

B. Kaplan-Meier curves for long-term mortality (with 95% CI) after hospital discharge. The colors of the quintiles correspond to colors as depicted in figure 1A. The highest UCE quintile had the best long-term mortality, which declined with declining baseline UCE (log-rank test: $P < 0.001$).

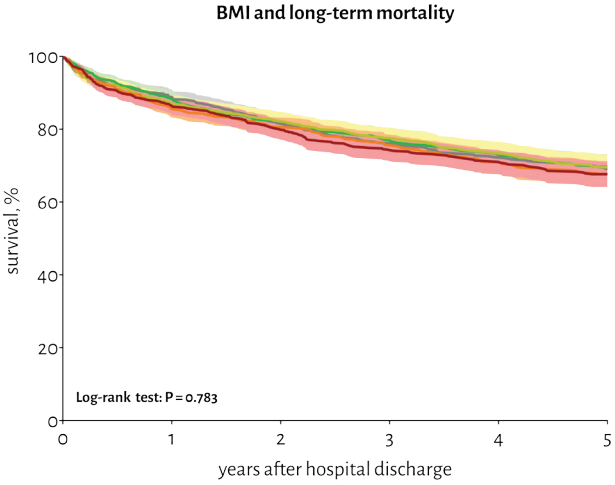


**Figure S6. Association between long-term mortality and BMI.**

Kaplan-Meier curves for long-term mortality (with 95% CI) after hospital discharge. The colors of the quintiles correspond to colors as depicted in figure 1A . BMI quintiles (*Q1*: red; *Q2:orange; Q3:yellow; Q4:green; Q5:gray*) did not discriminate for long-term mortality (log-rank test: $P = 0.783$).

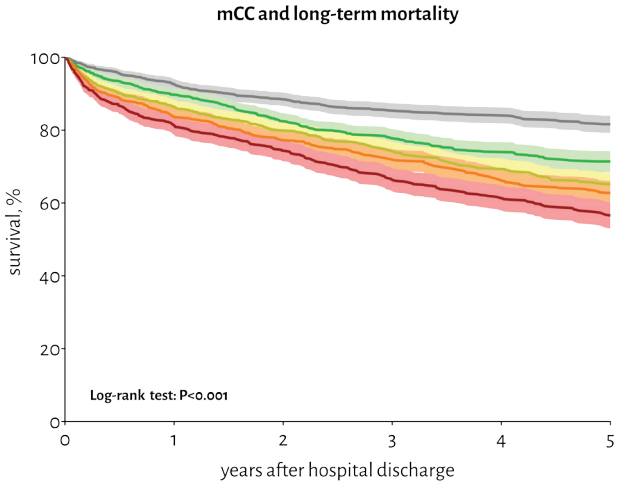


**Figure S7. Association between long-term mortality and mCC.**

Kaplan-Meier curves for long-term mortality (with 95% CI) after hospital discharge. The colors of the quintiles (Q1: red; Q2:orange; Q3:yellow; Q4:green; Q5:gray) correspond to colors as depicted in figure 1A. The highest mCC quintile had the best long-term mortality, which declined with declining baseline mCC (log-rank test: $P < 0.001$).

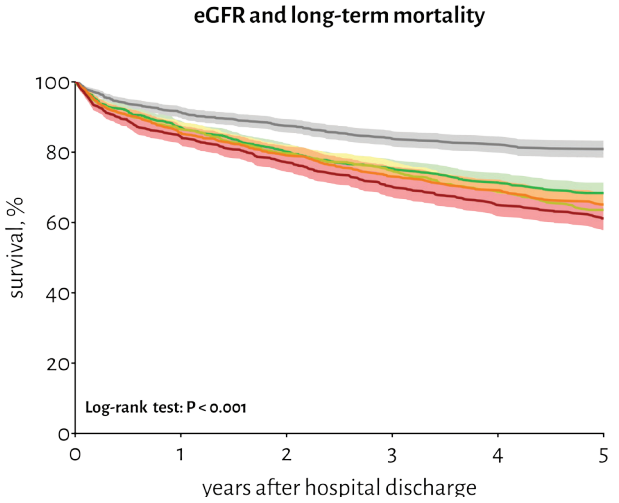


**Figure S8. Association between long-term mortality and eGFR.**

Kaplan-Meier curves for long-term mortality (with 95% CI) after hospital discharge. The colors of the quintiles correspond to colors as depicted in figure 1A (*Q1*: red; *Q2:orange; Q3:yellow; Q4:green; Q5:gray*). The highest eGFR quintile had the best long-term mortality, which declined with declining baseline eGFR (log-rank test: ($P < 0.001$).

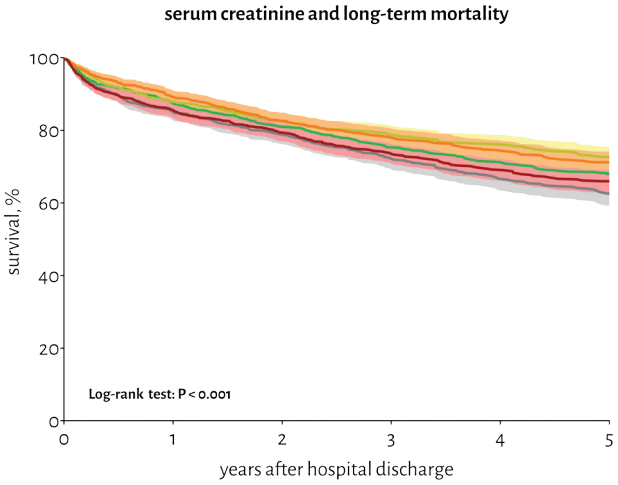


**Figure S9. Association between long-term mortality and serum creatinine.**
Kaplan-Meier curves for long-term mortality (with 95% CI) after hospital discharge. The colors of the quintiles correspond to colors as depicted in figure 1A (*Q1*: red; *Q2:orange; Q3:yellow; Q4:green; Q5:gray*). The lowest serum creatinine quintile had the best long-term mortality, which declined with rising baseline serum creatinine (log-rank test: $P < 0.001$).

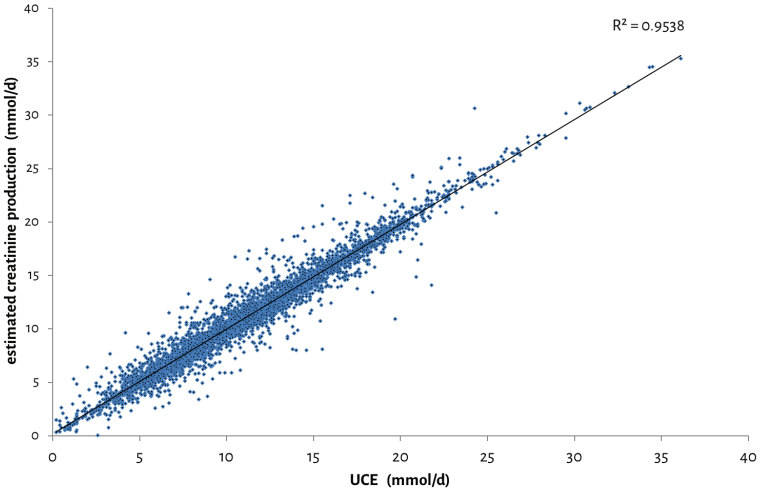


**Figure S10. Correlation between estimated creatinine production and UCE.**
Scatterplot of estimated creatinine production and UCE. Estimated creatinine production and UCE were highly correlated ($R^2$=0.954).

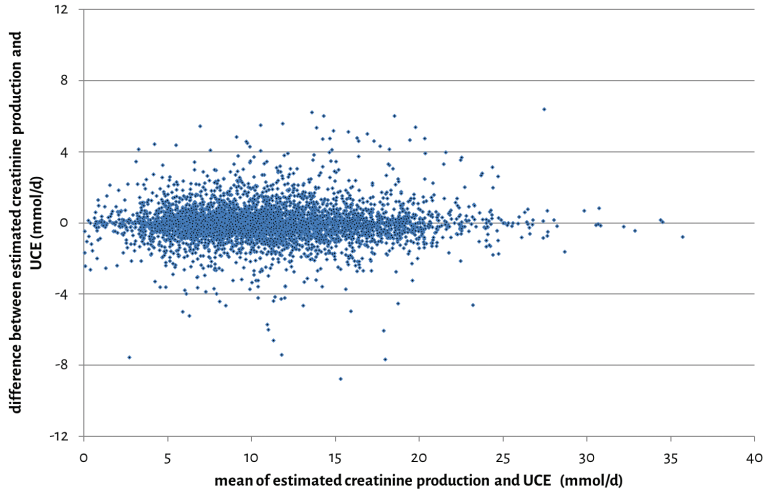


**Figure S11. Bland-Altman analysis of estimated creatinine production and UCE.**
Estimated creatinine production and UCE were depicted in a Bland-Altman plot. The mean difference between estimated creatinine production and UCE was -0.04±1.05 24h.

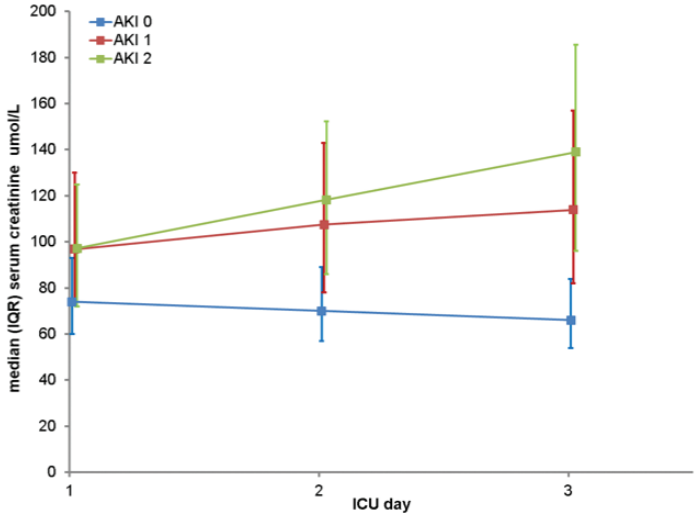


**Figure S12. Median serum creatinine over the first 3 ICU days in patients without or with AKI.**
Median (IQR) serum creatinine depicted per AKI stage for the first 3 ICU days. Serum creatinine was significantly lower in patients without AKI ($P < 0.001$).

# SUPPLEMENTARY REFERENCES


1. Bjornsson TD. Use of serum creatinine concentrations to determine renal function. Clin Pharmacokinet 1979;4:200-22.
2. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. Lancet 2002; 359: 1309–10.

# CHAPTER 10

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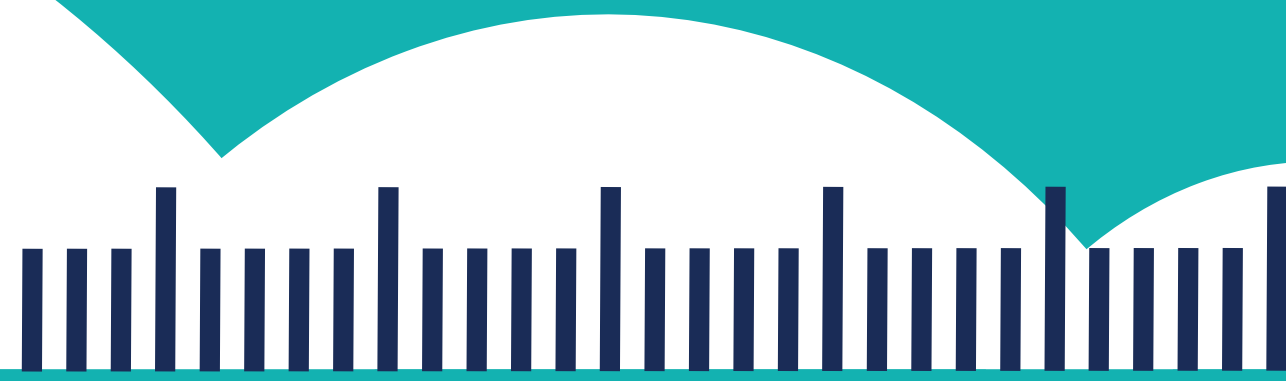
# TIME COURSES OF URINARY CREATININE EXCRETION, MEASURED CREATININE CLEARANCE AND ESTIMATED GLOMERULAR FILTRATION RATE OVER 30 DAYS OF ICU ADMISSION



**Submitted**

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## ABSTRACT

### PURPOSE

Urinary creatinine excretion (UCE) reflects muscle mass, and is strongly associated with ICU outcome. Since the combined time courses of serum creatinine, UCE, measured creatinine clearance (mCC) and estimated glomerular filtration rate (eGFR) during prolonged ICU admission have not been reported, we studied these parameters.

### METHODS

Over a 14-year period, patients with an ICU-stay ≥30 days and sufficient UCE measurements were evaluated. We excluded patients with stage 3 acute kidney injury. Additionally, we calculated mCC, estimated creatinine clearance according to Cockcroft-Gault and eGFR according to MDRD (modification of diet in renal disease) and CKD-EPI (chronic kidney disease epidemiology collaboration) equations.

### RESULTS

We included 248 patients with 5,143 UCE and 7,170 serum creatinine measurements. Hospital mortality was 24%. Over 30 days, UCE in male survivors and non-survivors decreased by 0.19 (95%CI 0.17-0.21; $P < 0.001$) and 0.16 (0.14-0.19; $P < 0.001$) mmol/d/d ($P = 0.18$) respectively. In female survivors and non-survivors, UCE decreased by 0.10 (95%CI 0.09-0.12; $P < 0.001$) and 0.05 (95%CI 0.02-0.07; $P < 0.001$) mmol/d/d ($P = 0.007$). The relative decreases in UCE were similar in all four groups: 1.3, 1.4, 1.2 and 0.9%/d respectively ($P = 0.39$).
Over the 30 day period, mCC remained unchanged, but eGFR increased by 31% (CKD-EPI; $P < 0.001$) and 73% (MDRD; $P < 0.001$). Creatinine clearance estimated by Cockcroft-Gault increased by 59% ($P < 0.001$).

### CONCLUSIONS

The rate of UCE decline during the first month of ICU stay corresponds to a muscle mass loss of more than 1% per day. This similar rate of decline in survivors, non-survivors, males and females underscores the intransigent nature of muscle wasting in the ICU. The use of eGFR to estimate renal function becomes progressively more inappropriate during ICU stay.

# INTRODUCTION

ICU patients typically display considerable muscle loss during critical illness, and lower muscle mass is associated with an increased mortality and morbidity incritically ill patients [1-3]. However, the time course of muscle mass loss during ICU admission remains poorly explored.

A non-invasive and low-cost method to estimate muscle mass is urinary creatinine excretion (UCE). Recently, baseline UCE, as a marker for muscle mass, was demonstrated to be strongly associated with mortality in a large cohort of ICU patients [4], and another study reported a decreased UCE at ICU discharge in patients with a prolonged ICU admission [5]. However, both studies did not describe the time course of UCE and related parameters during ICU admission.

UCE measurements are routinely performed in our ICU to determine measured creatinine clearance (mCC), since this may be a more accurate indicator of renal function than creatinine alone or formulas that estimate the glomerular filtration rate (eGFR) [5-7]. Moreover, prolonged critical illness and loss of muscle mass may be expected to lead to decreases in serum creatinine [5, 6, 8], which could further confound the assessment of renal function with eGFR. Consequently, the use of eGFR equations in patients with prolonged ICU stay might result both in overestimation and underestimation of renal function or so-called augmented renal clearance [9, 10], possibly leading to inadequate drug dosing [11].

The objective of this study was to describe the time course of UCE in critically ill patients with an ICU stay of at least a month. Over the same period the changes of mCC, estimated creatinine clearance according to Cockcroft-Gault and eGFR over time were assessed and compared to identify potential underestimation or overestimation of renal function.

# MATERIALS AND METHODS

## STUDY SETTING, PATIENT SELECTION AND OUTCOME

This study was a sub analysis of a recently published study in patients admitted for ≥24h to our ICU between 2002 and 2016 [4]. From these patients, we selected those with an ICU-stay of ≥30 days and for whom sufficient 24-h urine samples were available. Sufficient was defined as having at least 4 UCE measurements of which the first measurement was done at ICU day 1 to 3 and the last measurement in the final week of ICU admission. Patients with acute kidney injury (KDIGO-AKI) stage 3 (i.e., increase of serum creatinine to >300% from baseline, or ≥354 µmol/L or requiring RRT [12]) during the first 30 days were excluded. UCE was calculated by multiplying the urinary creatinine concentration in the 24-h urine with the 24-h urine volume. In case of missing UCEs, values were linearly interpolated over a maximum of 4 missing UCEs. Serum creatinine values were not interpolated. As males are known to have considerably higher UCE than females, we separately examined the UCE times courses for the two sexes.
This study was approved by our hospital's medical ethical committee and since it concerned an analysis of anonymized laboratory and clinical data, all collected during standard clinical care, informed consent was not required (METc 2011/132).

## FORMULAS

The mCC was calculated as 694 · UCE/serum creatinine ml/min. We also used the Cockcroft-Gault formula to estimate creatinine clearance, with sex, age and weight as input variables [13]. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) formula and according to the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula [14, 15] which both use serum creatinine, sex, and age as input variables.

Body surface area (BSA) was calculated as 0.007184 · (weight$^{0.425}$ · height$^{0.725}$). Augmented renal clearance was defined as either an mCC ≥130 ml/min, which is the preferred method [9], or an eGFR (MDRD and/or CKD-EPI) ≥ 130 ml/min/1.73m2. As we analysed UCE in 24h urine collections, we expressed the changes in UCE per day as changes in mmol per day per day, i.e., mmol/d/d.

## STATISTICAL ANALYSIS

Normally distributed data is expressed as mean (SD) and skewed data as median (IQR). A Chi-square test for categorical variables, Student's *t*-test for normally distributed continuous variables or a Mann-Whitney *U*-test for skewed distributed continuous variables were performed to determine differences between two groups. When more groups were compared, a one-way ANOVA or Kruskal-Wallis test was performed where appropriate.

The time course of UCE and renal function was estimated by a linear regression model through individual patient points. The intercept of the linear regression function was considered as the baseline value of UCE, glomerular filtration or creatinine clearance. Differences between slopes of linear regressions were compared with the *emmeans* package in *R*.

Additionally, we studied UCE over the first 90 days of ICU admission. As not all patients had an ICU stay of more than 90 days, not all patients fully contributed to the 90 days. Further subgroup analyses were performed in patients who developed AKI and patients who did not develop AKI and patients with augmented renal clearance. We also conducted analyses in which we analysed UCE per kilogram.

*P* values were considered to be significant when they were less than 0.05.

Data was analysed with *R* version 3.5.1. (R Foundation for Statistical Computing, Vienna, Austria).

**Table 1. Patient characteristics and outcome**

| | Survivors | Non-survivors | *P* |
|---|---|---|---|
| Sex, female | 70 (37.0) | 17 (28.8) | 0.318 |
| Age, year | 58.0 (42.0, 68.0) | 65.0 (53.5, 74.0) | 0.003 |
| Reason for admission (%) | | | 0.042 |
| Medical | 24 (12.7) | 7 (11.9) | |
| Abdominal/vascular surgery | 46 (24.3) | 13 (22.0) | |
| Neurosurgery | 4 (2.1) | 1 (1.7) | |
| Transplant | 8 (4.2) | 2 (3.4) | |
| Cardiothoracic surgery | 19 (10.1) | 7 (11.9) | |
| Trauma | 33 (17.5) | 1 (1.7) | |
| Miscellaneous | 55 (29.1) | 28 (47.5) | |
| ICU LOS, days | 40.74 (34.80, 52.86) | 42.98 (34.89, 65.20) | 0.155 |
| Hospital LOS, days | 64.08 (52.06, 83.47) | 55.73 (40.39, 76.34) | 0.039 |
| APACHE-IV | 65.00 (51.50, 77.00) | 83.00 (63.00, 96.00) | 0.006 |
| Length, cm | 175.00 (170.00, 182.00) | 178.00 (169.50, 185.00) | 0.616 |
| Weight, kg | 80.00 (70.00, 90.00) | 76.00 (65.00, 90.00) | 0.169 |
| BMI | 26.12 (23.12, 29.39) | 23.94 (22.07, 27.72) | 0.038 |
| BSA | 1.97 (1.82, 2.14) | 1.92 (1.75, 2.11) | 0.379 |
| Acute kidney injury[a] | | | 0.414 |
| No AKI | 89 (47.1) | 22 (37.3) | |
| Stage 1 | 61 (32.3) | 23 (39.0) | |
| Stage 2 | 39 (20.6) | 14 (23.7) | |
| Stage 3 | 0 (0) | 0 (0) | |

Mean (SD) or medians (IQR) are presented.

aAcute kidney injury was determined for the whole study period (i.e., the first 30 days of ICU admission) All patients with AKI stage 3 were excluded from analysis.

APACHE, Acute Physiology Age Chronic Health Evaluation.

## RESULTS

Of a total of 6,151 patients, 5,903 patients were excluded because of an ICU admission shorter than 30 days or an insufficient urine collection, 14 patients were excluded because of AKI stage 3 during the study period and 40 patients were excluded because of missing urine samples in the last 5 days of the study period (Supplementary Material: Figure S1). In the remaining 248 patients (Table 1), a total of 6,641 UCEs values were used, of which 1,498 (23%) were interpolated. 7,170 serum creatinine values (28.9 per patient) were used for the same period. In addition, another 1,026 UCE values were determined between day 30 and 90.

The median age was 60 (47-70) years and 87 (35%) patients were female. The median ICU LOS was 41 (35-54) days and the hospital LOS was 63 (48-83) days, with a hospital mortality of 24%. The median time that the hospital non-survivors died after ICU admission was 50 (39-74) days, with a range of 30-222 days.

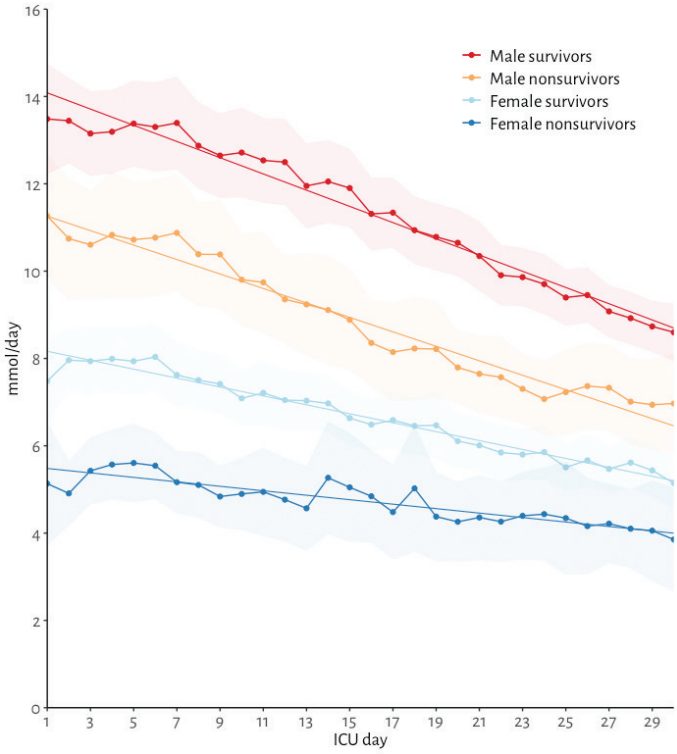


**Figure 1. Course of UCE in surviving and non-surviving males and females during the first 30 days of ICU stay.**
Males are depicted in blue and females in red. The dots represent the mean values, whereas the light shaded errors bars represent the 95%CI.
The respective regression formulas are:
Male survivors: UCE = -0.19 (95%CI -0.20;-0.17) ICU day + 14.34 (95%CI 14.01-14.67).
Male non survivors: UCE= -0.16 (95%CI -0.19; -0.14) ICU day + 11.52 (95%CI 11.10-11.94)
Female survivors: UCE = -0.10 (95%CI -0.11;-0.09) ICU day + 8.26 (95%CI 8.01-8.52)
Female nonsurvivors : UCE = -0.05 (95%CI -0.07; -0.02) ICU day + 5.56 (95%CI 5.18-5.93)

## TIME COURSE OF UCE

The mean UCE at admission was 11.6 (95%CI 11.3-11.8) mmol/d and was significantly higher compared to the mean UCE at day 30 (7.1 (95%CI 6.9-7.3) mmol/d, $P < 0.001$).
Mean UCE on admission, as was determined with linear regression, was 57% higher in males compared to females (13.6 (95%CI 13.3-13.9) vs 7.7 (95%CI 7.5-8.0) mmol/d, $P < 0.001$) as was UCE at day 30 (8.2 (95%CI 8.0-8.5) vs. 5.0 (95%CI 4.8-5.3) mmol/d, $P < 0.001$).

Linear regression analysis showed that UCE decreased by 0.18 (95%CI 0.16-0.20) mmol/d/d in males and by 0.09 (95%CI 0.08-0.10) mmol/d/d in females respectively ($P < 0.001$), equivalent to a 1.2 to 1.3%/d decrease of UCE compared to baseline UCE for both sexes.
Survivors had higher initial UCE's than non-survivors, and UCE showed a linear decrease in survivors of 0.16 (95%CI 0.14-017) mmol/d/d and of 0.13 (95%CI 0.11–0.15) mmol/d/d in non-survivors ($P = 0.05$), equivalent to a decrease of 1.3%/d compared to the baseline UCE in both groups

The course of UCE in survivors and non-survivors was also separately studied in males and females (Figure 1). Baseline UCE was significantly higher in surviving female patients (8.3, 95%CI 8.0-8.5 vs. 5.6, 95%CI 5.2-5.9 mmol/d respectively, $P < 0.001$). UCE at day 30 remained significantly different with a mean UCE of 5.2 (95%CI 5.0 – 5.5) mmol/d for female survivors and a mean UCE of 4.2 (95%CI 3.8-4.6) mmol/d for female non-survivors, $P = 0.02$. In female survivors, UCE showed a linear decrease of 0.10 (95%CI 0.09-0.12) mmol/d/d, whereas in female non-survivors, UCE showed a linear decrease of 0.05 (95%CI 0.03-0.07) mmol/d/d ($P < 0.001$).

Also in male patients, admission UCE was significantly higher in survivors (14.3, 95%CI 14.0-14.7 vs. 11.5, 95%CI 11.1-11.9 mmol/d respectively, $P = 0.001$). At day 30, UCE remained significantly different with a mean UCE of 8.8 (95%CI 8.5-9.1) mmol/d in male survivors and a mean UCE of 6.7 (95%CI 6.2-7.1) mmol/d in male non-survivors ($P = 0.003$). UCE showed a linear decrease of 0.19 (95%CI 0.17-0.21) mmol/d/d in male survivors and a decrease of 0.16 (95%CI 0.14-0.19) mmol/d/d in male non-survivors ($P = 0.18$).

The relative decreases in UCE were similar for male survivors, male non-survivors, female survivors and female non-survivors:1.3, 1.4, 1.2 and 0.9%/d, respectively ($P = 0.39$).

## MEASURES OF RENAL FUNCTION DURING 30 ICU DAYS

As muscle wasting may lead to overestimation of kidney function, we studied various methods of kidney function assessment (Figure 3). Over the course of 30 days, measured creatinine clearance (mCC) remained similar (0.004; 95%CI -0.18; +0.19, $P = 0.97$).

Changes in the other kidney function assessments were more extreme. Serum creatinine showed a linear decrease of 1.11 (95%CI -1.24; -0.98) ml/min. Estimated glomerular filtration according to the CKD-EPI formula showed a linear increase of 0.85 (95%CI 0.74-0.95) ml/min/1.73m2. Creatinine clearance predicted according to the Cockcroft-Gault formula was more extreme with a linear increase of 2.07 (95%CI 1.80-2.35) ml/min. When eGFR was measured with the MDRD formula, the observed linear increase was even more profound (2.22, 95%CI 1.97-2.47) ml/min/1.73m$^2$.

## ADDITIONAL AND SENSITIVITY ANALYSES

Figure 3 demonstrates the course of UCE over the first 90 days of ICU admission of the included ICU patients. As some ICU patients had shorter ICU stays, not all 248 patients fully contributed to the 90 days.

Additional analyses concerning the role of AKI, augmented renal clearance and weight are shown in the Supplementary material.

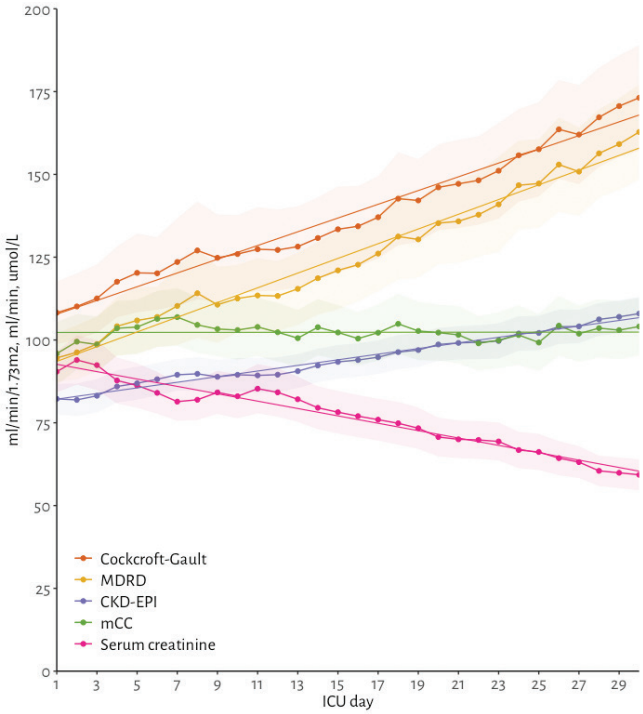


**Figure 2. Different measures of kidney function over the course of 30 ICU days.**

The eGFR according to the CKD-EPI and MDRD formulas are depicted in ml/min/1.73m2. Measured creatinine clearance and creatinine clearance according to the Cockcroft-Gault formula are depicted in ml/min. Information on weight was not available for the whole study cohort, this figure depicts the renal function of 196 (79%) patients with available information on weight. The dots represent the mean values, whereas the light shaded errors bars represent the 95%CI.

The respective regression formulas are:

Cockcroft-Gault = 2.07 (95%CI 1.80-2.35) ICU day + 105.71 (95%CI 100.85-110.56) (ml/min)

MDRD = 2.22 (95%CI 1.97-2.47) ICU day + 91.32 (95%CI 86.93-95.72) (ml/min/1.73m2)

CKD = 0.85 (95%CI 0.74-0.95) ICU day + 81.29 (95%CI 79.41-83.18) (ml/min/1.73m2)

mCC = 0.004 (95%CI -0.18; +0.19) ICU day + 102.30 (95%CI 99.03-105.50) (ml/min)

Serum creatinine = -1.11 (95%CI -1.24;-0.98) ICU day + 93.78 (95%CI 91.46-96.10) (umol/L)

## DISCUSSION

This study shows that urinary creatinine excretion (UCE), as a measure of muscle mass, steadily decreased over the first 30 days of prolonged ICU admission. Although baseline UCE differed between groups, the observed relative decrease in UCE of more than 1% per day was similar in survivors, non-survivors, males and females. Since creatinine levels also decreased over this period there is a progressive overestimation of renal function as estimated by Cockcroft-Gault, MDRD and to a lower extent by the CKD-EPI equation.

Our current study is the first paper to detail the time course of UCE during ICU admission. The absolute rate of change in UCE appeared to be primarily dependent on the absolute baseline value, as reflected by the stronger absolute decline in males compared to females and a stronger decline in survivors than non-survivors. Apparently, those with more muscle mass have

more potential to lose muscle mass. When the relative decrease in UCE was computed, the mean value varied between 0.9 and 1.4%/d between the four mentioned groups ($P = 0.39$). This finding corresponds with earlier observations. In a long-term follow-up study of patients with chronic kidney disease stage 3 and 4, UCE also steadily decreased at a fixed, albeit much slower, relative rate. In these patients, UCE was independently related to kidney failure and mortality and patients showed an approximate decline in UCE of 1.5% in UCE per year [16]. Several other studies in critically ill patients, which measured muscle mass mainly by ultrasonography, reported a decrease in muscle mass between 1 and 3%/d [1,17-20].

The decrease in UCE only appeared to reach a plateau after 50 days. Such a plateau phase or even an increase of the UCE might appear earlier in patients with only a brief ICU stay and clear clinical recovery afterwards, but this assumption should be verified in further studies.

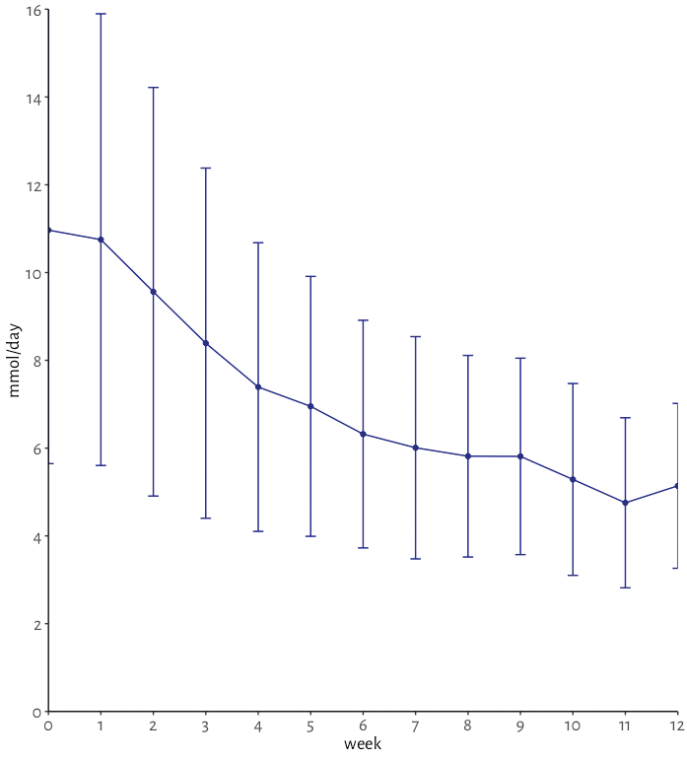


**Figure 3. Course of UCE over the first 90 days of ICU admission.**

ICU days are divided over weeks. Week 0 consist of the first 3 ICU days, whereas week 1 consists of day 4 – day 10 etc. Day 12 consists of day 80 to day 90.

Data is represented as mean UCE (SD).

There appears to be a rapid decline in UCE in the first 50 days. Only after 50 days a plateau phase seems to appear.

In contrast to the measured creatinine clearance (mCC) which utilizes UCE and serum creatinine, estimates that are only based on serum creatinine are still used far more often. The Cockcroft-Gault equation was developed to predict creatinine clearance without laboratory determination of urinary creatinine [13]. The MDRD study equation was developed for the assessment of GFR in CKD patients [14]. This was followed by the design of the CKD-EPI equation, which was meant to be an improved method for the assessment of GFR in patients with and without CKD, since the earlier developed MDRD study formula tended to underestimate measured GFRs at higher levels [15].
In our patients, the estimated GFR and estimated creatinine clearance equations falsely indicated an incremental rise in GFR which was most prominent for the MDRD-equation (Figure 2). Absolute overestimation was most striking for the Cockcroft-Gault equation and least pronounced for CKD-EPI. The Cockcroft-Gault equation already overestimated creatinine clearance at baseline. This formula was developed in 1976 when obesity was not as prevalent as today [21]. Although the inaccuracy of estimated renal function has long been known [5, 7, 22], our data underscores that the overestimation of GFR rapidly worsens as during prolonged ICU admission accompanied by decreasing muscle mass and creatinine production.

As a consequence, except for mCC, we saw that the various measures of renal function also progressively overestimated the incidence of augmented renal clearance (Supplementary material, SFigure 4). Its incidence increased from 20% at day 0 to 53% at day 30 when based on MDRD study equation and increased from 7% to 27% based on the CKD-EPI equation.

Apparently, ongoing loss of muscle mass is difficult to inhibit or even modify during critical illness [22]. Although muscle wasting obviously is related with outcome, the current results do not point to a novel clinical intervention strategy since we do not possess the tools to inhibit the muscle wasting despite our best efforts to optimally feed the patients [2, 24-26].

Our study confirms that glomerular filtration equations should not be used in critically ill patients. The MDRD-study and CKD-EPI eGFR equations were not designed for evaluating renal function in ICU patients [14, 15], nevertheless these formulas still frequently used in the ICU. They do not only progressively falsely suggest renal recovery and underestimate the actual CKD stage during ICU stay, but also put patients at risk for drug dosing errors since renal function is not correctly estimated [5]. Measured creatinine clearance through UCE in the 24h urine is thus the most reliable method to assess renal function in this patient group. To our knowledge, only few ICUs routinely measure UCE.

UCE is a non-invasive and easy method to estimate muscle mass [27], which shows a strong association with mortality in both critical ill and non-critical ill patient groups [4, 28, 29]. Other methods to measure muscle mass have been used in ICU patients [30]. Bioelectrical impedance represents a non-invasive method, but is not very suitable in ICU patients due to its requirement for fluid homeostasis [31]. Repeated ultrasonography can detect muscle wasting [17-20], but because of the lack of a common protocol, interpretation remains difficult [32]. Future studies in which changes in UCE is compared with ultrasonography in a larger study population would be interesting.

A limitation of our study is its post hoc design as well as the long study period. A potential limitation are the common changes in glomerular filtration rate in ICU patients which influence

UCE [10, 33]. UCE might also increase as a consequence of augmented renal clearance, but the persistent linear decrease we observed in UCE does not suggest this. The actual incidence of augmented renal clearance on ICU day 1 was low (13%), when mCC, corrected for BSA, was used to define GFR (Supplementary Material: Figure S4). Frequently prescribed drugs, such as diuretics and vasopressors may alter glomerular filtration rate [34,35]. Because UCE cannot be assessed in anuric patients, we excluded patients with AKI stage 3. Estimated GFR values were compared to measured creatinine clearance, which is not the gold standard for GFR assessment but is reliable in ICU patients when overestimation caused by possible increased tubular creatinine excretion is taken into account [7]. Muscle mass estimation by measurement of UCE requires a complete 24-h urine collection. Because a large majority of ICU patients have urine catheters and our ICU nurses collect 24-h urine in all patients on a daily base, the risk of collecting errors is reduced. Creatinine levels can be increased by meat intake. However, this was not a potential confounding factor in our study, since all our patients received enteral or parenteral feeding without any meat or added creatine.

In conclusion, UCE steadily decreases during the first month of ICU admission. During this period males, females, survivors and non-survivors showed the same relative decrease in UCE, underscoring the difficulty in reducing muscle mass loss in the ICU. Muscle wasting leads to a progressively worse performance of equations that estimate creatinine clearance or GFR when compared to actually measured creatinine clearance. We believe that use of the UCE improves assessment of muscle mass and also constitutes a superior tool to monitor renal function.

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# TIME COURSES OF URINARY CREATININE EXCRETION, MEASURED CREATININE CLEARANCE AND ESTIMATED GLOMERULAR FILTRATION RATE OVER 30 DAYS OF ICU ADMISSION

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## CHAPTER 10

Supplementary material

## FIGURES

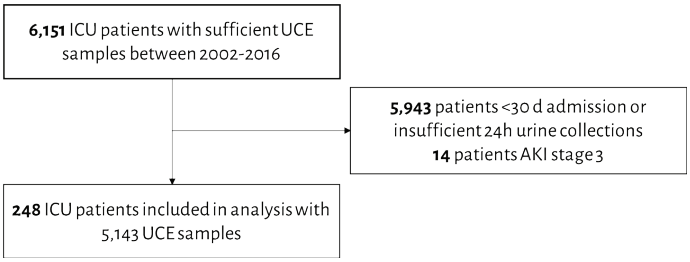



**Figure S1. Flowchart of patients included into the analysis.**

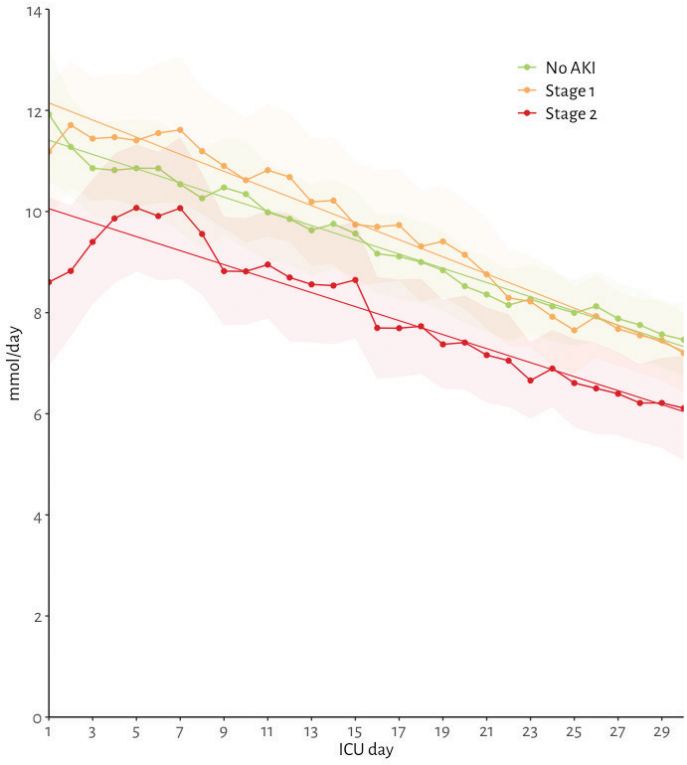



**Figure S2. Course of UCE during the first 30 days of ICU admission in patients with and without AKI.**

AKI was determined throughout the whole study period.

The dots represent the mean values, whereas the light shaded areas represent the 95%CI.

The respective regression formulas are:

No AKI : UCE = -0.14 (95%CI -0.16; -0.12) ICU day + 11.55 (95%CI 11.22-11.87)

Stage 1. UCE = -0.17 (95%CI -0.19; -0.14) ICU day + 12.31 (95%CI 11.89-12.74)

Stage 2. UCE = -0.14 (95%CI -0.16; -0.11) ICU day + 10.43 (95%CI 10.02-10.84)

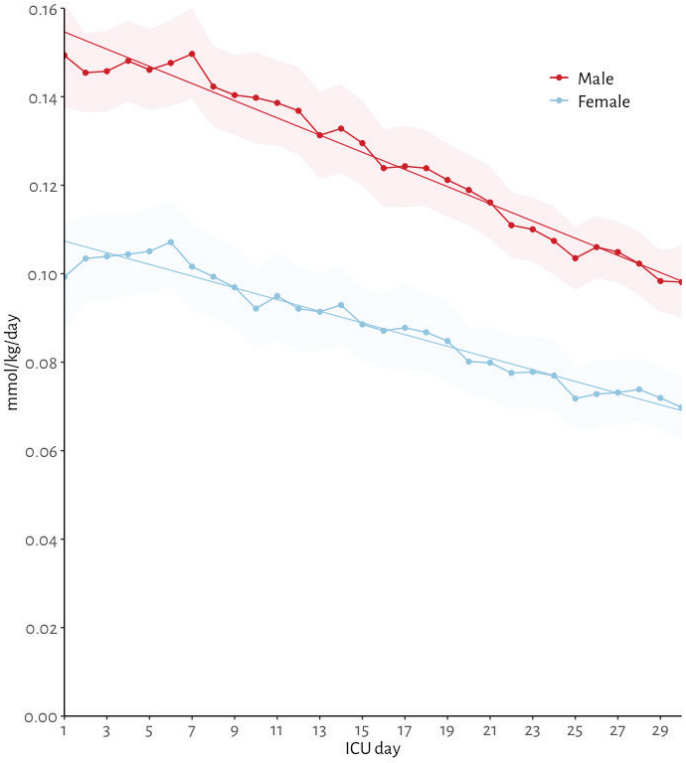


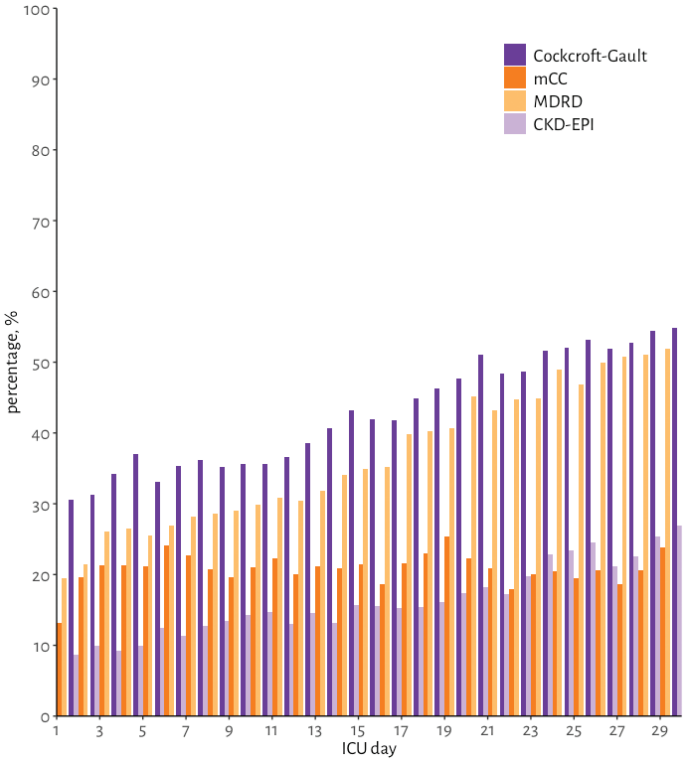

**Figure S3. Course of UCE in UCE/kg for the first 30 days of ICU admission.**

Information on weight was not available for the whole study cohort, this figure depicts the renal function of 196 (79%) patients with available information on weight. The dots represent the mean values, whereas the light shaded areas represent the 95%CI.

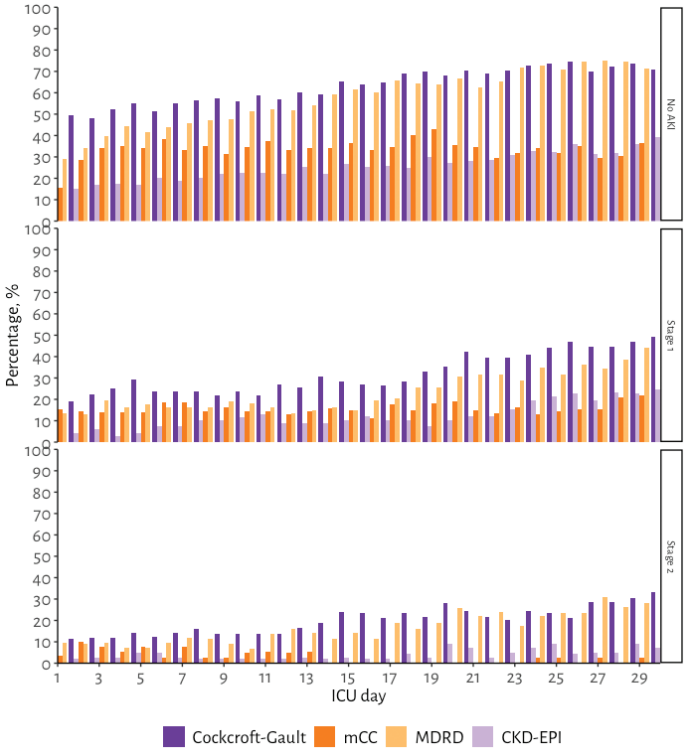
The respective regression formulas are:

Male: UCE = -0.0019 (95%CI -0.0020; -0.0017) ICU day + 0.158 (95%CI 0.155-0.161)

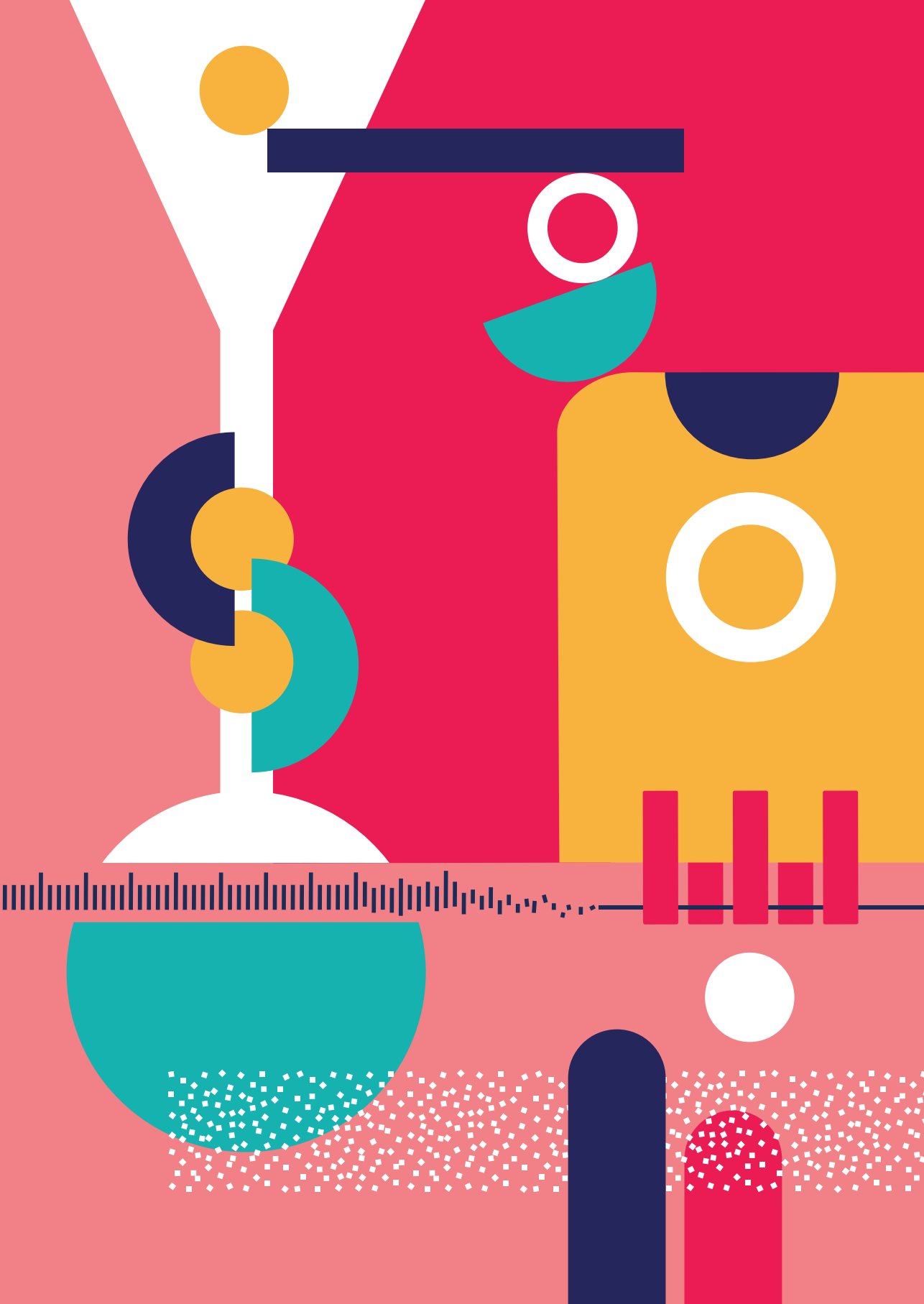
Female: UCE = -0.003 (95%CI -0.0015-0.0011) ICU day + 0.109 (95%CI 0.105-0.120)




**SFigure 4. Incidence of augmented renal clearance per measure of kidney function.**
Percentage of patients with augmented renal clearance (defined as >130 ml/min/1.73m2) per ICU day is depicted. In this figure, mCC is corrected for BSA. Information on BSA was not available for the whole study cohort, this figure depicts the renal function of 196 (79%) patients with available information on weight.




**SFigure 5. Incidence of augmented renal clearance per measure of kidney function per stage of AKI.**
Percentage of patients with augmented renal clearance (defined as >130 ml/min/1.73m2) per ICU day is depicted. In this figure, mCC is corrected for BSA. Information on BSA was not available for the whole study cohort, this figure depicts the renal function of 196 (79%) patients with available information on weight. Acute kidney injury was assessed on every ICU day, classification was based on the highest AKI stage for each individual patient during admission.



# CHAPTER 11

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SUMMARY

Critical illness is accompanied by changes in body composition, such as an increase of the extracellular volume and a contraction of the intracellular volume.
The research described in this thesis aimed to address a better understanding of these changes and corresponding biochemical derangements that critically ill patients experience during their illness.

In **Chapter 2**, we evaluated the association between derangements in circulating potassium levels and outcome and described the effect of the introduction of a computerized potassium regulation protocol (GRIP-II, Glucose and potassium Regulation in Intensive Care Patients). A before-after analysis was performed in more than 10,000 patients of whom 45% were regulated by GRIP-II. We found that hypokalemia, hyperkalemia and potassium variability were all independently associated with increased in-hospital mortality. Implementation of GRIP-II was effective and led to a significant decrease in potassium derangements.

**Chapter 3** describes the results of the GRIP-COMPASS trial. In this trial, we compared the effect of two different potassium targets - that were both within the normal range - on the postoperative incidence of atrial fibrillation and flutter. Potassium levels in both arms were regulated by the GRIP-II computer algorithm. The normal-low target was 4.0 mmol/L, the normal-high target was 4.5 mmol/L. Patients assigned to the high-normal target received significantly (73%) more potassium, mean potassium concentrations were only marginally different (4.22 mmol/L vs. 4.33 mmol/L, $P < 0.001$, respectively). There was no significant difference in the incidence of atrium fibrillation or flutter between the two groups (38% vs. 41% respectively).

In **Chapter 4** we further explored the remarkable intransigence of potassium levels despite the strongly different doses of potassium that were administered. In this chapter we performed comprehensive fluid and electrolyte balance studies in cardiothoracic surgery patients. Daily water, sodium and potassium balances were separately determined. The electrolyte free water (EFW) component of the water balance was also calculated. We found that rapid and profound volume and electrolyte administration resulted in a strongly positive fluid and sodium balance (4.0 ±0.6L and 814 ±75 mmol), but in a negative potassium and EFW balances (-101 ±14 mmol and -1.1 ±0.2L) over the first 4 days of ICU admission. This observation suggests that in contrast to conventional theory, the ICV remains constant or even decreases in critically ill patients, while the ECV rapidly expands.

In **Chapter 5**, we applied the same balance methodology to measure potassium and sodium shifts in human liver grafts and the relation of these shifts with graft viability. If potassium derangements occur after reperfusion during conventional liver transplantation, i.e., without an ex vivo perfusion phase, hyperkalemia is expected. Ex vivo perfusion with dual hypothermic oxygenated machine perfusion (DHOPE) improves graft function. We studied the effect of DHOPE on potassium and sodium shifts in ex situ and in vivo models. In both models, we observed increased potassium uptake by hypothermic machine perfused livers after reperfusion, which led to a decrease in blood potassium levels. Conversely, DHOPE-preserved livers showed a higher sodium output compared to conventional preserved livers. High potassium uptake was associated with a better viability of the liver graft.

Preservation of intracellular potassium may also be important to maintain skeletal muscle mass. Muscle wasting is an important complication of several chronic diseases, such as heart failure, and independently related to lower survival. The addition of angiotensin and aldosterone inhibitors to standard therapy has led to a profound increase in survival in heart failure patients. In **Chapter 6** we stated our hypothesis that the potassium sparing nature of these inhibitors may lead to an increase in total body potassium and therefore to a preservation of skeletal muscle mass. If this medication does indeed lead to an increase in total body potassium has to be demonstrated by either potassium balance studies or 40K scintigraphy.

We described long-term changes in the incidence of dysnatremia in the intensive care and its association with mortality in **Chapter 7**. In this chapter, we studied all sodium measurements of two university hospital ICUs over a 21-year period. We observed a striking shift in the pattern of ICU-acquired dysnatremias: the incidence of hyponatremia almost halved (47% to 25%, $P < 0.001$), whereas the incidence of hypernatremia almost doubled (13% to 24%, $P < 0.001$). Severe dysnatremia was significantly associated with higher mortality. We concluded that the higher incidence of hypernatremia is probably due to changes in therapy and therefore often ICU-acquired. ICU-acquired hypernatremia should thus be preventable and its incidence may therefore be considered as indicator of quality of care.

There is some evidence that sodium can be stored without expansion of the extracellular volume (ECV) (i.e., nonosmotically). This phenomenon has been described in various patient groups, but has not yet been demonstrated in critically ill patients. In **Chapter 8** we aimed to identify the possibility of nonosmotic sodium and chloride storage with balance studies. We used meticulously recorded fluid, sodium and chloride balances of the first 4 ICU days. The balances could not account for 296 mmol (111 to 566 mmol) of sodium and 243 mmol (62 to 471 mmol) of chloride during this period. We were the first to describe missing osmotically active chloride in humans. We suggest that the apparent disappearance of both considerable amounts of sodium and chloride from the extracellular space, might result from movement into the ICV, without invoking non-osmotic storage. The exact mechanism behind the disappearance of sodium and chloride certainly requires further study.

Muscle mass is an important determinant to survive critical illness and is associated with morbidity and mortality in critically ill patients, but it is difficult to quantify in ICU patients. Many methods, such as MRI, CT or anthropometric measures, are not suitable for usage in the ICU. Urinary creatinine excretion (UCE) as a surrogate for muscle mass, has been shown to be strongly associated with mortality in various patients groups. However, it has not been evaluated in the critical ill. In **Chapter 9** we studied the relation of baseline UCE excretion with short-term and long-term mortality in critically ill patients. We included 6,151 patients with 11,198 UCE measurements. We found that in ICU patients without severe renal dysfunction, low urinary creatinine excretion at ICU admission is strongly and independently associated with both short-term and long-term mortality. This underscores the importance of low muscle mass as risk factor in ICU patients and the relevance of UCE as a possible biomarker.

Critical illness induces loss of muscle mass, which can add up to more than 10% in the first week of ICU admission. It has been observed earlier that prolonged ICU admission leads to a decrease in both UCE and serum creatinine. However, the time course of UCE during ICU admission has not been described in detail. Also the time courses of estimated renal function as calculated by various frequently used formulas, that often use serum creatinine as input variable, have not been described. In **Chapter 10** we studied the time courses of UCE, measured creatinine clearance, estimated creatinine clearance and estimated glomerular filtration rate (according to the Modification of Diet in Renal Disease (MDRD), Chronic Kidney-Epidemiology Collaboration (CKD-EPI), and Cockcroft-Gault equations). We included a total of 248 ICU patients, with 5,143 UCE and 7,170 serum creatinine measurements.
Over 30 days, the relative decrease in UCE was similar for male, female, survivors and non-survivors (1.3, 1.4, 1.2, and 0.9%/d, respectively, $P = 0.39$). We also observed that both the eGFR and estimated creatinine clearance equations became progressively more unreliable during ICU stay. Our findings underscore the intransigent nature of muscle wasting in critically ill patients. The use of UCE may improve assessment of muscle mass and might be superior in monitoring renal function.

# CHAPTER 12

# GENERAL DISCUSSION

The maintenance of a constant volume and composition of body fluids is essential for homeostasis. Many mechanisms that allow the maintenance of homeostasis have been unraveled. However, there remains much to discover about the acute changes in the fluid and electrolyte compartments in critically ill patients.
In this thesis, we aimed to improve the understanding of the measured biochemical derangements and associated underlying changes in body composition during critical illness. This chapter discusses our main findings and identifies potential future research areas.

## CATABOLISM IN CRITICALLY ILL PATIENTS

During the first week, a critically ill patient can lose up to 10% of his total lean body mass [1]. Muscle mass is the result of a balance between protein synthesis and breakdown. Critical illness induces marked proteolysis to guarantee a sufficient supply of amino acids to support the synthesis of acute phase proteins and other components of the systemic inflammatory response. This protein imbalance leads to rapid muscle wasting [1].
Due to the loss of muscle mass as well as muscle function, survivors of critical illness can experience significant muscle weakness, which can persist for years [2]. Although more information on the extent of muscle wasting has been gained over the last years, current methods to quantify and monitor and ultimately reduce muscle wasting are cumbersome or inaccurate.

### THE IMPORTANCE OF BASELINE MUSCLE MASS

Most studies focus on the magnitude of the catabolism that accompanies critical illness, but the muscle mass itself at the onset of critical disease may be an important determinant of the ability of patients to overcome their ICU stay as well. Low muscle mass on ICU admission is independently associated with morbidity and mortality in critically ill patients [1,3]. However, it is still difficult to quantify muscle mass in this patient group, as measures to assess muscle mass are generally poorly suited for ICU patients [4,5]. Anthropometric measurements, such as BMI, waist circumference, mid-arm or mid-thigh muscle measurements are often hampered by the presence of edema, ascites or dehydration. More advanced techniques, such as computer tomography (CT) and magnetic resonance imaging (MRI) are invasive and expensive and not practical for routine use in ICU [6]. Repeated ultrasonography of well-defined muscle parts to measure baseline muscle mass and detect subsequent muscle wasting appears to be a more promising technique. However, this technique also has its limitations and there is no universal protocol yet to measure muscle mass with this method [7].

In various patient groups, urinary creatinine excretion (UCE) has shown to be an easy and inexpensive method to assess muscle mass [8-10]. We showed in Chapter 9 that baseline 24-h UCE, as a marker of muscle mass, is associated with both short-term mortality and long-term mortality in critically ill patients. Although we did not use other measures to assess muscle mass, and therefore could not verify the assumption that UCE solely reflects muscle mass, baseline UCE was a very strong predictor of outcome.

In **Chapter 10** we subsequently show that UCE declines during ICU stay in patients who were admitted to the ICU for longer than 30 days. A decrease in UCE during ICU stay was suggested earlier [11]. In this earlier study, the UCE on the day of discharge was lower in long-stay ICU

patients (i.e., more than 7 days) compared to patients who stayed for a relatively short period in ICU. Unfortunately, this study did not have any data on the baseline UCE. Our study was therefore the first to actually show the gradual but very considerable decrease in UCE during ICU stay.

## IDENTIFYING THE ACUTE STRESS PHASE IN CRITICALLY ILL PATIENTS

Loss of muscle mass and consequently muscle function is a major long-term consequence of critical illness and hugely affects quality of life after ICU admission.
The metabolic stress response can be divided into a catabolic (acute) phase and an anabolic (post-acute) phase. The start and end of these phases are not embedded in stone and are different in every patient. Also the occurrence of a new derangement during critical illness, such as a second episode of sepsis, can induce the start of a new catabolic phase [12].
Identification of the current metabolic phase of a patient might be useful to successfully intervene. Interventions, such as nutrition, may be more helpful in the post-acute phase [13]. Over the last years, several studies have investigated the impact of the timing, dose, constitution and route of feeding in the critically ill [14,15]. However, to date there is no universally accepted standard of care defined. One of the challenges is to differentiate the acute phase from the post-acute phase and thus identify a phase in which a patient is possibly ready for enhanced feeding.

A dynamic marker that shows the catabolic rate from day to day could aid in developing nutritional strategies that are based on metabolic signals rather than on a predefined number of days [16,17]. The potassium balance in critically ill patients might be such a dynamic marker (**Chapter 4**).

Since the vast majority of potassium resides intracellularly, negative balances indicate the loss of ICV during catabolism. If the potassium balance becomes neutral or even positive, this may indicate that the patient is beyond the catabolic phase and may even be anabolic. This knowledge may be used to adapt feeding strategies.
Recently, balances from other intracellular elements have been studied. It has been argued that next to potassium, also phosphate balances may provide information on the presence of catabolism [12,18]. In critically ill children, phosphate balances were shown to be even more accurate than potassium balances [18]. Phosphate balances have not been investigated in critically ill adults and thus have to be studied in this population.

Nitrogen balances are traditionally used to assess the protein balance [19]. They have the disadvantage that total urinary nitrogen has to be calculated from urinary urea nitrogen. Urinary urea nitrogen is assumed to constitute 80 to 90% of the total urinary nitrogen and this can lead to underestimation of the nitrogen excretion in situations with increased excretion of non-urea forms of nitrogen, such as ammonium. This might lead to a false-positive nitrogen balance. Total urinary potassium and phosphate on the other hand can be directly measured. Potassium and potentially phosphate balances could serve as an easy obtainable marker to get more insight in the current phase of the metabolic stress response of a critically ill patient.

Balance studies themselves have other disadvantages [20-22]. They represent events in the preceding 24 hours, causing a delay in information. However, this can be overcome by performing balance studies covering a shorter time period. Possible shorter time periods could be 12

hours, 6 hours or even 2 hours. Covering shorter time periods could lead to a more "real-time" assessment of (new) catabolic events. A requirement to conduct such shorter balance studies is adequately timed urine sampling.

## THE CONSTANCY OF THE INTRACELLULAR COMPARTMENT

General physiology models depict the ICV and the ECV as two compartments that are both quite flexible in size. Free water and electrolytes are distributed among the two compartments, leading to an equilibrium. Maintaining a constant ICV, however, is critical for cellular homeostasis [23,24]. Cellular volume changes affect many critical metabolic and signaling processes. Many life forms have developed mechanisms to stabilize the ICV. One of these mechanisms is to rapidly adjust the concentration of osmoles inside the ICV with the help of so-called osmolytes [23,26]. These are intracellular molecules, can be generated on short notice to avoid shrinking or swelling by adjusting to intracellular osmolarity to that of the environment. In **Chapter 4**, a relative constancy or even immediate shrinkage of the ICV in critically ill patients was observed. It was already known that critically ill patients who receive large amounts of fluid retain water and sodium in the ECV. However, this detailed balance study showed that there was a negative potassium balance next to fluid and sodium retention. Although the water balance was strongly positive, the electrolyte-free water (EFW) balance was negative. A decrease of the ICV has been earlier reported in patients after trauma [27]. In these patients, a reduction of TBK and intracellular water was observed, but intracellular potassium concentration remained similar. The loss of body potassium in parallel with the reduction of the ICV is the result of muscle mass loss. An important clinical consequence is that the assumption that administered electrolyte free water (e.g. glucose 5%) does distribute equally over the ECV and ICV in proportion to their relative volumes is not correct.

### VIABILITY OF LIVER GRAFTS

The liver serves as an important physiological buffer for enteral potassium loads. The cellular uptake of a potassium load requires active transport by Na+/K+-ATPase [28]. During procurement of liver grafts, lower temperatures are used to reduce the graft's metabolic requirements and its need for oxygen. Reduced active transport of sodium and potassium then occurs, but passive transport of potassium is facilitated [29]. As a consequence the reperfusion of a liver graft is typically accompanied by hyperkaliemia in the recipient. However, a new technique to preserve the liver graft (DHOPE), led to hypokalemia in recipients after reperfusion. During DHOPE liver grafts undergo hypothermic oxygenated perfusion [30]. Liver grafts show increased intrahepatic ATP-levels during DHOPE through the oxygenation of the perfusion fluid whilst they have been ATP-depleted because of previous ischemia. The low temperature during perfusion assists in this restoration of ATP levels [30].

In **Chapter 5** we compared potassium and sodium shifts in liver grafts transplanted after the liver graft was preserved by the conventional and the DHOPE technique. We observed significantly higher ATP-levels in DHOPE livers after reperfusion. High ATP-levels significantly correlated with a decrease in recipient serum potassium levels upon reperfusion. Also, increased recipient potassium levels correlated with high peak ALT. A decrease in serum potassium might therefore be an useful marker of early function of liver grafts. The observed decrease in serum potassium was mirrored by an increase in serum sodium, which emphasizes the proper early function of the $Na^+/K^+$ pump.

## SODIUM DERANGEMENTS IN THE CRITICALLY ILL

In **Chapter 7** we showed that hypernatremia is often iatrogenic and associated with mortality. Infusion with sodium-based fluids, although used on a routine basis, are thus not without danger. Sodium-based fluids are commonly used in clinical practice as it is believed that only these fluids will expand the ECV, without significant and unwanted expansion of the ICV [31]. Other fluids, such as glucose/saline mixtures, are believed to distribute among both compartments. However, in **Chapter 4**, we were not able to demonstrate any increase in the ICV by rapid infusion of large fluid volumes. As homeostasis aims for a constant ICV, the conventional theory that fluid will distribute evenly among the compartments until equilibrium is to be questioned. Further studies are needed to investigate if different fluid regimens, such as sodium-free solutions, do indeed have the same effect as sodium-based infusion fluids.

## A SUB-COMPARTMENT IN THE EXTRACELLULAR COMPARTMENT?

Recently, the accumulation of hypertonic sodium in peripheral tissues such as the skin has been reported [32,33]. This remarkable claim challenges the conventional assumption on the distribution of sodium. A sub-compartment of the extracellular compartment, in which sodium is stored non-osmotically, was postulated. In this "sub-compartment", sodium is presumably bound to glycosaminoglycans in the skin. The role of chloride, the major circulating anion, in this postulated mechanism is unclear. Although the exact clinical significance of such a possible non-osmotic storage mechanism has not been verified, it might be related with hypertension [34,35]. The existence of non-osmotic sodium storage has been studied in varied patient groups, but not in critically ill patients.

In **Chapter 8** we demonstrated with balance studies a significant disappearance of both sodium and chloride in critically ill patients. We were the first to demonstrate this phenomenon in this patient group. However, our study was not designed to identify the location of the missing sodium and chloride. One of the possibilities is that this missing sodium and chloride is indeed stored non-osmotically in tissues such as the skin and muscle. A major problem with this explanation is that no plausible mechanism for non-osmotic chloride storage exists. However, another key alternative is movement of sodium and chloride into the ICV [36]. Patients in **Chapter 8** were known to have a negative potassium balance, which might point towards the possibility of sodium redistribution toward the ICV. In healthy volunteers, it has been demonstrated that muscle damage can lead to accumulation of sodium and chloride in the intracellular compartment [37]. As critically ill patients often suffer from critical illness myopathy, this might also be a possible scenario.

# FUTURE PERSPECTIVES

## CATABOLISM IN CRITICALLY ILL PATIENTS

This thesis provides several new potential markers to gain more insight into the changes in body composition during critical illness.

As it remains difficult to assess muscle mass and therefore to assess the impact of muscle mass wasting on survival, UCE could serve as an adequate surrogate. It is possibly an easy assessment of muscle mass to accurately identify low muscle mass at baseline. UCE provides important prognostic information and might possibly improve prognostic scores. Validation of our findings should be performed in large multicenter studies. Ideally, adequate adjustments for renal function and other techniques to assess muscle mass should be compared.

Potassium balances, and potentially phosphate balances as well, could aid the intensivist in providing nutritional or other support. This could be adjusted to the corresponding metabolic phase of the patient and therefore tailored support can be provided.
A combination with UCE might even provide more information on nutritional success [18]. Balances could also serve as a secondary endpoint in nutrition trials. Balances are an relatively easy method, with the only challenge that urine samples have to be adequately collected.

## THE CONSTANCY OF THE INTRACELLULAR COMPARTMENT

New techniques to adequately preserve, and to even enhance, the function of the liver graft before transplantation are being developed. A decrease in potassium levels upon reperfusion might be a good marker of ATP function in liver grafts. Future studies are necessary to confirm the utility of potassium levels as an early marker of liver function.

The water and salt homeostasis in critically ill patients remains a very challenging topic. The existence of a possible non-osmotic storage should be further studied, with more thorough techniques such as 23Na and 39Cl MRI or skin biopsies. However, even with these advanced techniques, it is difficult to differentiate signals from the intracellular and extracellular compartment. MRI is now unfortunately only able to detect the total 23Na signal and does not differentiate between fluid compartments.
Nonetheless, regardless of the existence of a sub-compartment, the need to explore the increased use of infusion fluids that contain less or no sodium is obvious.

## CONCLUSION

Changes in body composition due to critical illness remain intriguing. We showed that urinary creatinine excretion provides important prognostic information. Potassium balances are possibly a good marker to immediately demonstrate and quantify loss of ICV and may provide assistance in guiding nutritional therapy. More than 150 years after Claude Bernard introduced the concept of the milieu intérieur, we can still conclude that the constancy of the intracellular compartment is of utmost importance. The ability of the liver graft to retain its potassium intracellularly might be a good early marker of liver graft function. The postulated existence of a sub-compartment in which sodium (and chloride) are nonosmotically stored requires further proof. Increased use of infusion fluids such as glucose 5% may not be as detrimental for volume resuscitation in critical disease as previously assumed.

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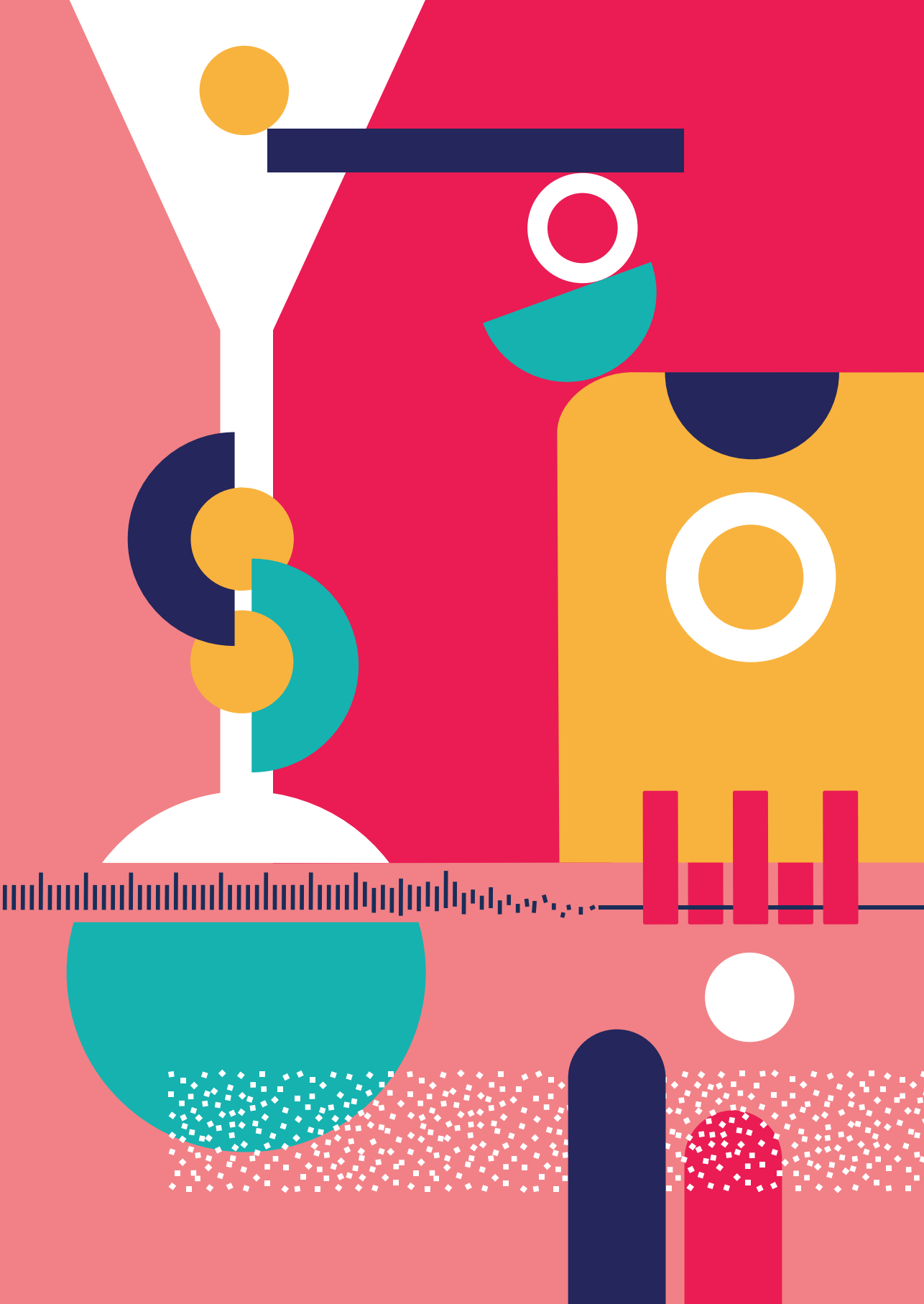

# HOOFDSTUK 13

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NEDERLANDSE SAMENVATTING

DANKWOORD

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Dit proefschrift beschrijft de invloed van acute ziekte op de water- en zouthuishouding en de daardoor optredende veranderingen in de lichaamssamenstelling.
Water- en zoutstoornissen komen vaak voor bij acuut zieke patiënten. Dit kan zowel door de ziekte zelf komen, als door de behandeling. Het is niet altijd bekend wat de betekenis is van de afwijkingen die optreden in de water- en zouthuishouding. Ook is het niet altijd duidelijk of de prognose van de patiënt verbetert door deze afwijkingen te corrigeren.

Om de verdeling van water en de zouten kalium en natrium over het lichaam beter te begrijpen, wordt het lichaam vaak in twee compartimenten verdeeld. Dit zijn het intracellulaire en het extracellulaire compartiment. Het intracellulaire compartiment omvat alle lichaamscellen en normaal bevindt grofweg 66% van het lichaamswater zich in dit compartiment. Het extracellulaire compartiment bestaat uit twee delen: het bloed en het vocht rondom de cellen. In het intracellulaire compartiment bevindt zich voornamelijk het zout kalium. In het extracellulaire compartiment bevindt zich voornamelijk natrium.

In **Hoofdstuk 1** wordt een kort overzicht geschetst van de onderzoeksdoelen van dit proefschrift en de bestaande literatuur over dit onderwerp.

Precieze regulatie van de kaliumconcentratie in het bloed is van groot belang. Bij ernstig zieke patiënten kan er sprake zijn van een te hoog of te laag kaliumgehalte in het bloed. Dit kan ernstige gevolgen hebben, zoals hartritmestoornissen. In **Hoofdstuk 2** wordt de relatie tussen de kaliumconcentratie in het bloed en de kans op overleven van ernstig zieke patiënten beschreven. Daarnaast beschrijven we het effect van de regulatie van de kaliumwaarde in het bloed door middel van een computergestuurd algoritme, Glucose en kalium Regulatie in Intensive Care Patiënten (GRIP-II). Dit deden we door de kaliumregulatie vóór en nadat we dit algoritme in gebruik namen te vergelijken. We onderzochten in totaal 10,000 intensive care (IC) patiënten, waarbij de kaliumconcentratie van 45% van deze patiënten gereguleerd werd door GRIP-II. Zowel een verhoogde, een verlaagde, alsmede de variatie in kaliumwaarden waren geassocieerd met een verhoogde sterfte gedurende de ziekenhuisopname. Het implementeren van GRIP-II leidde tot een verlaging van het aantal afwijkende kaliumwaarden.

Op de intensive care wordt getracht om de kaliumconcentratie in het bloed binnen de normaalwaarden te houden om onder andere hartritmestoornissen te voorkomen. Het is echter onbekend of een “laag-normale” (4.0 mmol/L) of juist een “hoog-normale” (4.5 mmol/L) kaliumconcentratie bij patiënten na een openhartoperatie effectiever is met betrekking tot de preventie van hartritmestoornissen. Een computergestuurd kaliumprotocol biedt de mogelijkheid om eenvoudig twee verschillende kaliumstreefwaarden met elkaar te vergelijken. In **Hoofdstuk 3** hebben we twee genoemde kaliumconcentraties en het effect op het voorkomen van boezemfibrilleren vergeleken. Boezemfibrilleren is een hartritmestoornis die regelmatig optreedt na een openhartoperatie. Bij 910 patiënten bleek dat er tussen beide kaliumstreefwaarden geen verschil was in het ontstaan van boezemfibrilleren. Opvallend was wel dat, ondanks de 73% hogere kaliumtoediening in de “hoog-normale” groep, de kaliumspiegels in het bloed in beide groepen nagenoeg gelijk waren. Dit suggereert dat dit extra toegediende kalium snel uit de circulatie verdwijnt en vermoedelijk via de urine is uitgescheden.

In **Hoofdstuk 4** beschrijven we hoe we dit fenomeen verder onderzochten. We analyseerden uitgebreide vocht- en zoutbalansen van patiënten na een openhartoperatie. Bij een balansstudie wordt de gehele inname en het gehele verlies (bijvoorbeeld via de urine en drains) van patiënten verzameld. De verliezen worden van de inname afgetrokken en men houdt dan de balans over. Wanneer de inname even groot is als het verlies, is de balans dus nul.
We ontdekten dat patiënten na openhartchirurgie gedurende de eerste vier opnamedagen veel water en natrium vasthielden, terwijl er juist netto kalium werd uitgescheiden. Ook werd er zogenaamd "elektrolyt vrij water" verloren. Het volume van het extracellulaire compartiment, dat vooral natrium bevat, nam sterk in omvang toe bij patiënten na openhartchirurgie. Omdat we weten dat kalium in het lichaam zich voornamelijk in het intracellulaire compartiment bevindt, concludeerden we dat het kaliumverlies, samen met het elektrolyt-vrije water, uit dit compartiment moet komen. Het intracellulaire compartiment lijkt dus te krimpen gedurende acuut ernstige ziekte, mogelijk door het verlies van spiercelvolume.

**Hoofdstuk 5** beschrijft het gebruik van dezelfde balansmethode, maar ditmaal om de natrium- en kaliumverschuivingen in donorlevers te onderzoeken. Tegenwoordig wordt een nieuwe techniek gebruikt om de kwaliteit van donororganen te verbeteren. Hierbij wordt een geïsoleerd orgaan voorafgaand aan de transplantatie eerst een aantal uren op een machine aangesloten die een speciale, zuurstof bevattende vloeistof rondpompt. Normaal gesproken worden donorlevers kort gespoeld met een speciale vloeistof en vervolgens bewaard en vervoerd in ijs voordat ze getransplanteerd worden.
Het is bekend dat wanneer een lever getransplanteerd wordt en de bloedtoevoer vanuit de ontvanger met de donorlever is hersteld, de kaliumspiegel in het bloed van de ontvanger snel kan stijgen. Het transplantatieteam is hierop ingesteld en zal met gerichte maatregelen proberen de kaliumconcentratie weer te verlagen. Met geïsoleerde perfusie voorbehandelde behandelde levers bleken echter juist een daling in de kaliumspiegel te veroorzaken in de ontvangers.
We onderzochten de oorzaak van deze verschuivingen en ook onderzochten we of natrium- en kaliumverschuivingen geassocieerd kunnen zijn met de kwaliteit van de donorlevers. We vergeleken hiervoor 16 geïsoleerd geperfundeerde donorlevers met 18 "normale" donorlevers. Ook onderzochten we zowel levers die uiteindelijk niet getransplanteerd werden, als wel getransplanteerde levers.
De geïsoleerd geperfundeerde levers bleken reeds kalium uit te scheiden tijdens de perfusie op de machine. Nadat deze levers geïmplanteerd waren in ontvangers, namen deze levers weer kalium op zodra de bloedtoevoer hersteld was, waardoor juist een daling van de kaliumconcentratie in het bloed ontstond. Natrium gedroeg zich precies andersom en werd hierbij juist extra uitgescheiden. Waarschijnlijk is de aanvankelijke kaliumstijging het gevolg van het zeer hoge kaliumgehalte van de preservatievloeistof, hetgeen tijdens geïsoleerde perfusie van de lever wordt uitgescheiden. De daaropvolgende daling kan duiden op een goed functionerende donorlever, waarbij de lever kalium opneemt om het intracellulaire compartiment constant te houden.

Het behoud van het intracellulaire compartiment kan ook mogelijk een rol spelen in het behoud van spiermassa. Veel chronische ziektes, zoals hartfalen, kunnen leiden tot verlies van spiermassa. Dit verlies leidt tot een grotere kans op sterfte. De zogenaamde diuretica (plastabletten) die vaak onderdeel van de hartfalentherapie zijn, zorgen er voor dat meer kalium via de urine verloren gaat. Het toevoegen van aanvullende medicatie aan de oorspronkelijke therapie voor hartfalen, in de vorm van zogenaamde ACE-remmers en aldosteronantagonis-

ten heeft geleid tot een belangrijke toename van de kans op overleving in hartfalenpatiënten. In **Hoofdstuk 6** stellen wij dat deze toename in de kans op overleving mede het gevolg kan zijn van het feit dat deze medicamenten kaliumsparend werken en het totale lichaamskalium daardoor beter in stand gehouden wordt. Dit zorgt ervoor dat het intracellulaire compartiment ook niet overmatig krimpt. Een belangrijk onderdeel van het intracellulaire compartiment is spiermassa. Of ACE-remmers en aldosteronantagonisten daadwerkelijk leiden tot minder verlies van het totale lichaamskalium en spiermassa dient verder onderzocht worden. Dit zou met speciale technieken waarbij het totale lichaamskalium gemeten wordt (40K scintigrafie) of met balansstudies mogelijk moeten zijn.

Ook stoornissen in de natriumspiegel in het bloed kunnen leiden tot gevaarlijke complicaties. In **Hoofdstuk 7** beschrijven we op de IC opgetreden natriumstoornissen bij een grote groep IC patiënten, behandeld in Groningen en Rotterdam gedurende de afgelopen 20 jaar en onderzochten we de relatie van deze stoornissen met kans op overleving. Ernstige natriumstoornissen bleken geassocieerd te zijn met sterfte. We zagen verder dat er een opvallende verschuiving is opgetreden in het soort natriumstoornissen gedurende deze periode. In vergelijking met 20 jaar geleden komen verlaagde natriumspiegels nu voor bijna de helft minder voor, terwijl verhoogde natriumspiegels juist bijna dubbel zo vaak voorkomen. We denken dat deze verschuiving van verlaagde naar juist verhoogde natriumspiegels komt omdat we momenteel relatief meer natrium-houdende infuusvloeistoffen toedienen. Een belangrijk deel van de natriumstoornissen wordt dus veroorzaakt door de gegeven therapie en zou daarom ook voorkomen kunnen worden.

Vaak wordt verondersteld dat wanneer men veel natrium inneemt en vasthoudt, men ook meer vocht vasthoudt. Onlangs is echter beschreven dat het wellicht mogelijk is dat natrium opgeslagen wordt in de huid, zonder dat daarbij vocht wordt vastgehouden. Dit mogelijk nieuwe fenomeen is voor enkele patiëntgroepen beschreven, maar niet voor intensive care patiënten.
In **Hoofstuk 8** beschrijven we ons onderzoek naar dit fenomeen. We onderzochten of patiënten na openhartchirurgie natrium en chloor vast hielden zonder daarbij water vast te houden. Dit deden we wederom met de balansmethode, waarbij we de eerste 4 opnamedagen onderzochten. De onderzochte patiënten kregen gedurende deze periode veel natrium via het infuus toegediend, zo'n 8 gram per dag. Dit is ongeveer 4 keer meer dan de normale aanbevolen hoeveelheid in een gezond dieet. We ontdekten dat gedurende de studieperiode er zowel natrium als chloor "verdween" zonder dat daarbij water werd vastgehouden. Het ging hierbij om behoorlijke hoeveelheden, vrijwel gelijk aan het natriumchloride dat in twee liter infuusvloeistof zit. Wij zijn de eersten die dit fenomeen beschrijven met betrekking tot natrium bij intensive care patiënten, en de eersten dit met betrekking tot chloor beschrijven bij patiënten.
Of zout ook daadwerkelijk in de huid opgeslagen wordt, konden we met deze studie niet aantonen. Een alternatieve verklaring zou zijn dat het zout in het intracellulaire compartiment verdwenen is. Dit moet echter in vervolgonderzoek geverifieerd worden.

Spiermassa is een belangrijke prognostische factor voor de intensive care patiënt, maar we zijn nog niet goed in het meten van spiermassa in deze patiëntengroep. Veel methoden, zoals MRI en CT, zijn te lastig om uit te voeren bij deze ernstig zieke patiënten. Een eenvoudigere mogelijkheid is om creatinine, een afvalstof van spieren, te meten in de urine. Iedereen scheidt elke dag een min of meer stabiele hoeveelheid creatinine uit, welke evenredig is met de spier-

massa in het lichaam. **Hoofdstuk 9** beschrijft de associatie tussen creatinine in de urine gemeten tijdens de eerste dagen van de intensive care opname, als een surrogaat voor spiermassa, en de kans op overleving. We onderzochten hiervoor ruim 6000 IC patiënten met bijna 12.000 urine metingen. Creatinine uitgescheiden in de urine blijkt een sterke voorspeller van zowel de korte termijn als de lange termijn kans op overleving bij deze patiënten. Deze bevinding onderstreept het belang van spiermassa reeds bij aanvang van ernstige ziekte.

Acuut ernstige ziekte leidt tot het verlies van spiermassa. Dit kan oplopen tot meer dan 10% spiermassaverlies in de eerste week van de IC opname. Wanneer de hoeveelheid creatinine in de urine wordt gemeten, blijkt dat dit gedaald is in patiënten die langdurig op de intensive care hebben gelegen. Spiermassaverlies zorgt er tevens voor dat de creatininespiegel in het bloed lager wordt. De creatininespiegel in het bloed wordt op de IC veel gebruikt in formules om de nierfunctie in te schatten. Echter, het verloop van de hoeveelheid creatinine in de urine en de geschatte nierfunctie gedurende de intensive care opname is niet bekend.
**Hoofdstuk 10** beschrijft het verloop van zowel het creatinine in de urine, de gemeten nierfunctie als de geschatte nierfunctie gedurende de eerste 30 dagen van de IC opname. We onderzochten in deze studie 248 IC patiënten met meer dan 5000 creatinine metingen in de urine en ruim 7000 creatinine metingen in het bloed. De hoeveelheid creatinine uitgescheiden in de urine daalde aanzienlijk gedurende de studieperiode. Ongeacht geslacht en uitkomst van de opname, kwam deze daling overeen met ongeveer 1% spiermassaverlies per dag. Formules om de nierfunctie te berekenen lieten daarentegen een toenemende stijging van de nierfunctie zien, terwijl de gemeten nierfunctie gelijk bleef.
Deze formules zijn dus onbetrouwbaar op de intensive care, zeker wanneer een patiënt langdurig is opgenomen. De constante en gelijke daling van spiermassa benadrukt hoe moeilijk spiermassaverlies is te beïnvloeden in een ernstig zieke patiënt.

# HOOFDSTUK 13

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HET IS AF! BIJNA TIEN JAAR ONDERZOEK IS NU DAN EINDELIJK GEBUNDELD IN DIT PROEFSCHRIFT. EN OOK VOOR MIJ GELDT HET CLICH : IK HAD HET NIET ALLEEN KUNNEN DOEN. IK WIL GRAAG IEDEREEN DIE MIJ IN DE AFGELOPEN JAREN HEEFT GEHOLPEN BEDANKEN, EN EEN PAAR PERSONEN WIL IK GRAAG IN HET BIJZONDER NOEMEN.

**Dr. M.W.N. Nijsten**, beste Maarten. Dit boekje was er zonder jou niet geweest. Als jonge geneeskundestudent begon ik met een proefproject bij jou, dat via een wetenschappelijke stage uiteindelijk is uitgegroeid tot een MD/PhD traject. In al die jaren heb ik ontzettend veel van je geleerd. Ik denk dat weinig mensen de luxe hebben om één op één met hun promotor aan hun onderzoek te werken. Het samen analyseren van en discussiëren over onze bevindingen heb ik altijd als heel waardevol ervaren. Jouw kritische, maar ook nieuwsgierige manier van denken heeft dit proefschrift zeker naar een hoger niveau getild. Hopelijk heb ik die manier van denken een beetje over kunnen nemen. Dank je wel voor alles.

**Prof. dr. A.M.G.A. de Smet,** beste Anne Marie. Als promotor was jij meer betrokken bij de logistiek van mijn proefschrift. Met al onze plannen en ideeën was het soms heel fijn iemand te hebben om Maarten en mij eraan te herinneren dat we niet alle tijd van de wereld hadden. Daarnaast had je ook oog voor de persoon achter het promotietraject, wat ik erg gewaardeerd heb.

**Dr. M. Zeillemaker-Hoekstra**, beste Miriam. In mijn tweede jaar geneeskunde kwam ik jou als onervaren geneeskundestudent helpen met de dataverzameling voor de GRIP-COMPASS studie. Zeker door jouw vertrouwen in mij ben ik uiteindelijk het MD/PhD-traject in gerold en kon ik verder met jouw onderzoeksresultaten. Dank je wel voor de fijne begeleiding en de tips, en wat leuk om dit promotietraject uiteindelijk af te sluiten met jou als mijn copromotor!

Graag wil ik de beoordelingscommissie, **prof. dr. R. Bellomo, prof. dr. S.P. Berger** en **prof. dr. R.P. Pickkers**, bedanken voor het lezen en beoordelen van mijn proefschrift.

Last year I was given the opportunity to spend five months at the department of Critical Care, Austin Hospital, Melbourne, Australia under the supervision of prof. dr. R. Bellomo. Dear **Rinaldo**, thank you for the incredible months I got to spend at your department. I find the amount of time and care you personally invest in your research fellows admirable and it has definitely. It was an honor to be part of your team. I hope we will continue to work together in the future. Thanks to the research nurses and the other research fellows I felt immediately at home at the Austin. Thank you **Glenn** (Hi Glenn!), **Leah, Helen, Fumi, Laurent, Lisa** and **Tom**. I hope we meet again one day. **Eva**, wat is de wereld toch klein! Hoe leuk was het om een beetje (bekend) Nederland te hebben in Melbourne en de perikelen van een paar maanden onderzoek in het buitenland te kunnen delen. And last but not least: my more than wonderful housemates and friends: **Elizabeth Zhong** and **David Greenwood**. I couldn't thank you enough for the wonderful time we had. You really were my home away from home. We will see each other soon (Tour de France trip 2020?)!

**Prof. dr. Heleen Oudemans-van Straaten**, dank u wel dat u voor mij de deur naar Melbourne openzette. Zoals u destijds zei: het was de kers op de taart! Nadine, hopelijk publiceren we binnenkort ons BIA artikel. Bedankt voor de fijne samenwerking en als je tips over de BIA.

**Laura Burlage** en **prof. dr. Robert Porte**, het heeft even mogen duren, maar onze samenwerking heeft tot een prachtig artikel geleid waar ik nog steeds met trots op terug kijk! Laura, het was een plezier om met je samen te werken!

Ik zou graag de **Junior Scientific Masterclass** willen bedanken dat ze me de kans hebben gegeven om aan het MD/PhD traject te beginnen. **Jans**, bedankt dat ik altijd aan kon komen waaien voor vragen en om even gezellig te kletsen.
Mijn tijd op de intensive care was niet zo leuk geweest zonder alle collega's. Lieve leden van de **krokkettenclub**, dank jullie wel voor alle gezelligheid tijdens de lunch. Het was altijd weer thuiskomen bij jullie na een jaar coschappen. **Wim Dieperink**, dank je voor al je hulp, alle verhalen en je persoonlijke interesse. Lieve **researchverpleegkundigen**, ontzettend bedankt voor alle hulp met de BIA studie (sorry voor het CRF...) en voor alle momenten dat ik even bij jullie mocht komen buurten. **Elsa**, ik heb genoten van onze gesprekken over onze teckels! **Rene**, escalatievogel van de ICV. Wat een feest om je erbij te hebben. Soms moest ik streng voor je zijn (als je weer eens (on) opvallend mee liep te lezen!), maar bovenal bedankt voor alle gezelligheid en goede gesprekken over familietaferelen en carrières. Ik denk nog met veel plezier terug aan die avond in Wenen toen jij je opwierp als barman!
**Bart**, wat fijn dat we samen zowel onze MD/PhD struggles als onze liefde voor foute hitjes konden delen. **Annemieke**, dank je wel voor de fijne samenwerking toen wij nog als kalium/natrium-duo aan het werk waren. Ik ben heel benieuwd naar de uitkomsten van je ECLS onderzoek! **Meint**, wat leuk om met jou het enthousiasme voor urinemetingen te delen. Hoofdstuk 10 was hopelijk nog maar het begin!

HOEWEL IK AL JAREN VEEL TE DRUK BEN, HEB IK TOCH DE LUXE ONTZETTEND FIJNE VRIENDEN OM ME HEEN TE HEBBEN.

Lieve Westenholte-Stadshagen-Spoolde gang, Plomhies of hoe we tegenwoordig dan ook heten, lieve **Eline, Romy, Ellen, Marloes** en **Lotte**. Wat fijn dat ik in 5 vwo bij jullie ben aangehaakt. Zeker nu ik na al deze jaren zo een reünie van de Morgenster zou kunnen bijwonen of een willekeurig supermarktgesprek in Westenholte zou kunnen voeren, is het alsof ik er altijd bij ben geweest. Dank jullie wel dat jullie me zo thuis laten voelen in deze vriendengroep. Op nog vele jaren vriendschap!

Roerige bestuursjaren zijn de perfecte basis voor goede vriendschappen. Lieve Vera, wat fijn dat ik nog steeds bij jou en Erik-Jan aan mag schuiven voor een heerlijk eten en decaf koffie. Gelukkig komen we altijd om de een of andere reden dicht bij elkaar terecht. Laten we dit nog lang volhouden. Lieve **Fran**, ideale reispartner, wie weet plakken we ooit nog eens een reisje zonder man aan ons rijtje vast. Wat een feest om samen met jou tussen apen yoga te doen, onverstandig ijs te eten op Cuba en te treinen door Egypte. Het blijft jammer dat we niet dichterbij elkaar wonen, maar dat heeft ons nog nooit tegengehouden! Lieve **Els**, harde werker, ik kijk nu al uit naar jouw promotie. Dank je wel dat ik altijd bij je terecht kan en dat we elkaar zo goed kunnen vertellen hoe het wél moet. Lieve **Ish**, dat er nog maar veel saunadagjes mogen volgen. Hopelijk wonen we snel wat dichterbij elkaar. Groningen-Zwolle is maar een uurtje, dat is niets!

IFMSA bracht mij nog meer lieve vrienden. Lieve **Kris**, gelukkig zijn we na een slechte eerste indruk toch bevriend geraakt. Ik ben trots op je hoe je na jaren hard werken nu je plek met Lex in Enschede hebt gevonden. Lieve **Elise**, reeds dr. van der Stouwe bij mijn promotie, laten we nog lang lunchen/koffiedrinken/theetjes doen en onderzoekservaringen uitwisselen.

Lieve **Emmy**, lieve Ems, vriendinnen sinds jaar 1 tutorgroep. Jaren waarin we elke dag koffiedronken (terwijl jij netjes naar college ging en ik in de pauze even langskwam), nu iets meer afstand van elkaar hebben. Gelukkig houdt ons dat niet tegen!

Lieve Roadtrip XXS, **Lucas**, **Iris**, **Johan**, **Frank de W, Janita, Frank W, Amy,** dank jullie wel dat ik bij jullie mocht aansluiten. Sorry dat ik Rick naar het noorden heb gesleept. Op nog veel fietsweekendjes en gin-tonic/wijn avondjes!

Lieve **Eva**, Eef, een van de weinig zekerheden die ik in mijn leven heb is dat jij er bent. Ik ben supertrots op hoe jij je door de afgelopen jaren heen hebt geslagen. De aanhouder wint en dat ga jij sowieso doen! We zien elkaar ongetwijfeld uiteindelijk onverwachts in dezelfde vakgroep. En: die reis samen gaat er komen, hoe dan ook!

HET MOOISTE WAT IK AAN DEZE PROMOTIE OVER GEHOUDEN HEB IS UITEINDELIJK NIET DIT BOEKJE, MAAR EEN AANTAL HEEL DIERBARE VRIENDSCHAPPEN.

Lieve **Frank**, wat een mooie samenloop van omstandigheden dat ik bij jou op de kamer terechtkwam. Het heeft me mogelijk wel een aantal artikelen gekost, maar dat neem ik op de koop toe. De afgelopen jaren heb je me naast de nodige onzin ook door de nodige rottigheid gesleept en daar ben ik je ontzettend dankbaar voor. Wat ben ik blij dat je nu naast me staat. Lieve **Inge**, dank je wel voor je zorgzaamheid, de fijne wandelingen en dat ik altijd bij jou en Frank mag aankloppen. Lieve **Laurens**, vanuit Helmond kwam jij bij Frank en mij op de kamer, wat zeker de productiviteit niet verder bevorderde. Dank je voor alle grappen, sarcastische opmerkingen, maar ook voor de goede gesprekken. Ik ben erg dankbaar dat ik altijd op jou en Lis kan terugvallen in Ubbena. Met Rick die veel weg is, betekent dat veel voor me. Ik ben blij dat jij de tweede lange man bent die vandaag naast me staat. Lieve **Lis**, gelukkig ben je gestopt me te haten en kwamen we er daardoor achter dat we naast een deelbrein, ook motorisch redelijk op één lijn zitten. Goed om te weten dat er iemand net zulke idiote gedachten heeft als ik. Dat we nog maar heel vaak cactusvijgthee drinken of 96 euro aan cocktails mogen uitgeven!

Lieve **Ed** en **Franca**, dank jullie wel voor de warme ontvangst in jullie gezin, de belangstelling en de trots die jullie tonen. Lieve **Nien** en **Marij**, eindelijk twee zussen! **Nick** en **Henk**, wat een feest om jullie als mede-aanhang te hebben.

Lieve **papa** en **mama**, wat een gekke, roerige jaren zijn het geweest. Ook al is ons gezin nu 180 graden anders dan dat ik 10 jaar geleden had voorzien (en gehoopt), ik ben blij dat we nu een nieuwe balans hebben gevonden. Dank jullie wel voor de steun en het geloof in mij de afgelopen jaren. Papa, wat ontzettend leuk dat ik mijn boekje bij jou heb kunnen laten drukken! Lieve **Rienk** en **Karin**, dank jullie wel dat jullie mijn ouders gelukkig maken.

Lieve **Jelmer**, ik zeg het niet genoeg, maar ik ben ontzettend trots op je. Het is nog niet altijd makkelijk, maar jij komt er wel. Laten we snel een keer weer een broer-zus etentje doen!

Lieve **opa Jan**, **oma Petra** en **oma Fien**, wat fijn dat jullie er vandaag bij zijn! Lieve **opa Meindert**, wat ontzettend jammer dat we je al drie jaar moeten missen. Ik mis je en ben gek met je.

Lieve, lieve **Rick**. Waarom zullen we het ons makkelijk maken als het moeilijk kan? De afgelopen jaren zijn niet altijd gemakkelijk geweest en ik vermoed dat ik al enige tijd door de AIVD in de gaten gehouden word vanwege mijn dreigingen de marine plat te bombarderen als je weer eens weg moet. Maar je bent alles meer dan waard. Jij brengt de rust in mijn leven die ik nodig heb en steunt me onvoorwaardelijk. Ik kijk uit naar nog vele jaren met jou. Op naar de 96!

# HOOFDSTUK 13

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NEDERLANDSE SAMENVATTING

DANKWOORD

CURRICULUM VITAE

LIST OF PUBLICATIONS

Lara Hessels werd op 9 augustus 1991 geboren te Zwolle en groeide daar op met haar ouders en broertje. In 2009 behaalde zij haar atheneumdiploma aan het Carolus Clusius College te Zwolle, waarna zij begon aan haar studie geneeskunde aan de Rijksuniversiteit Groningen.

Gedurende haar studie was Lara actief bij de International Federation for Medical Students' Association (IFMSA), waar zij, na eerst in een aantal werkgroepen actief te zijn geweest, zowel een lokale als landelijke bestuursfunctie bekleedde. Tevens was zij als studentlid betrokken bij de ontwikkeling van het bachelor geneeskundecurriculum "G2020" en gaf ze als studenttutor onderwijs aan bachelorstudenten geneeskunde.

Sinds het eerste jaar van haar studie kwam Lara via de Junior Scientific Masterclass in aanraking met het doen van wetenschappelijk onderzoek. In het tweede jaar van geneeskunde startte zij met een proefproject naar kaliumregulatie op de intensive care onder leiding van dr. M.W.N Nijsten en dr. M. Zeillemaker-Hoekstra. Dit project resulteerde uiteindelijk in een MD/PhD traject. Tijdens dit traject alterneerde zij haar coschappen met het doen van fulltime wetenschappelijk onderzoek. Na de junior coschappen in het Universitair Medisch Centrum Groningen en het Ommelander Ziekenhuis te Winschoten, deed Lara haar senior coschappen in het Antonius Ziekenhuis te Sneek en het Medisch Centrum Leeuwarden te Leeuwarden. Uiteindelijk sloot zij haar studie geneeskunde af met haar semi-artsstage op de afdelingen infectieziekten en hematologie in het UMCG, die haar bevestigden in haar enthousiasme voor de interne geneeskunde.

Nadat het behalen van haar artsenbul in 2018, vertrok Lara voor een half jaar naar Australië om haar promotieonderzoek af te ronden op de intensive care van het Austin Hospital te Melbourne onder leiding van prof. dr. R. Bellomo. Gedurende dit half jaar was zij betrokken bij verscheidene multicenter studies en verrichte zij retrospectief onderzoek.

Sinds 1 juli 2019 is zij werkzaam als ANIOS interne geneeskunde in het Medisch Centrum Leeuwarden. Lara is getrouwd met Rick en samen wonen zij in Groningen.

# HOOFDSTUK 13

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NEDERLANDSE SAMENVATTING

DANKWOORD

CURRICULUM VITAE

LIST OF PUBLICATIONS

- **Hessels L**, Hoekstra M, Mijzen LJ, Vogelzang M, Dieperink W, Oude Lansink A, Nijsten MW. The relationship between serum potassium, potassium variability, and in-hospital mortality in critically ill patients and a before-after analysis on the impact of computer-assisted potassium control. Crit Care 2015;19:4.

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